# Tosufloxacin Versus Norfloxacin for Prevention of Infections in Chemotherapy-Induced Neutropenic Patients

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(Received February 8, 1994)
(Accepted: April 6, 1994)

Key words: norfloxacin, tosufloxacin, bacterial infection, prophylaxis, hematological malignancies

## Abstract

We conducted a non-randomized, prospective study comparing the efficacy of tosufloxacin with that of norfloxacin in preventing bacterial infection during chemotherapy-induced neutropenic episode. Fifty-one patients with hematological malignancies were included, and a total of 108 episodes of neutropenia were studied. There was no significant difference between the two groups in the incidence of fever, in the time-to-event analysis of febrile episodes nor in the incidence of gram-positive bacteremia despite the broader spectrum of tosufloxacin. The incidence of gram-negative bacteremia was lower in patients treated with the quinolones as a prophylactic than in the historical controls given polymyxin B. Especially the incidence of bacteremia due to *Pseudomonas aeruginosa* was significantly less when tosufloxacin was used. A possible synergistic effect of sulfamethoxazole-trimethoprim in preventing the febrile episode was also observed.

## Introduction

The prophylactic use of antibiotics to prevent bacterial infection from gastrointestinal tract during chemotherapy-induced neutropenia has been investigated by using polymyxin B and vancomycin or cotrimoxazole[1)~3)]. Because of the side effects of cotrimoxazole, such as prolongation of neutropenia and the emergence of resistant bacteria, fluorinated quinolones were then introduced and shown to be more effective than a placebo or cotrimoxazole[4)~7)].

Among the quinolones, ciprofloxacin, which has greater antibacterial activity than norfloxacin, was shown to be more effective in preventing febrile episodes than norfloxacin, even though the incidence of gram-positive bacteremia remained the same, partly because of their relative lack of activity against gram-positive bacteria[8)].

Tosufloxacin, another new quinolone, is more active against gram-positive bacteria than ciprofloxacin[9)]. It also has at least the same antibacterial activity against gram-negative bacteria[9)]. We therefore performed a non-randomized trial comparing tosufloxacin with norfloxacin in their ability to prevent bacterial infection in chemotherapy-induced neutropenia in patients with hematological malignancies, concentrating especially on the effect against gram-positive bacteria. We have also compared the isolated pathogens obtained from blood cultures to those obtained from the historical controls given polymyxin B as a prophylactic.

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## Materials and Methods

*Patients*

The eligible patients were 52 consecutive adults who had acute leukemia or malignant lymphoma, were hospitalized in the hematology division at the Tokyo Metropolitan Komagome Hospital between May 1990 and October 1992, and were expected to develop chemotherapy-induced neutropenia (less than $0.5 \times 10^9$/L) lasting more than 10 days.

*Prophylactic regimen*

The patients received norfloxacin, 200 mg three times a day, between May 1990 and October 1991. From November 1991 to September 1992, they received tosufloxacin, 300 mg twice a day. Prophylactic therapy was started on the day chemotherapy was initiated and was stopped when the neutrophil count exceeded $0.5 \times 10^9$/L. The patients were treated under conventional ward conditions or in a single room with a compact high-efficiency particulate air filtered laminar air flow (LAF) system (Bed Isolator IL30-S, Toyo Netsu Kogyo Kaisha, Ltd., Tokyo).

Trimethoprim-sulfamethoxazole (TMP-SMX; 80 mg of trimethoprim and 400 mg of sulfamethoxazole) was used three times a day, three times a week to prevent *Pneumocystis carinii* infection for all patients with lymphocytic malignancies and some with myelogenous leukemia. Central venous catheters were used in accordance with the decision of the responsible physicians. All patients were examined daily for clinical sings of infection and when the temperature increased to more than 38°C or when infection was suspected, at least two sets of blood cultures were obtained and treatment with systemic antibiotics consisting of broad spectrum penicillin or cephalosporin and aminoglycoside was initiated. Complete blood counts were made at least three times a week and blood chemistry studies once a week. The first day the neutrophil count became lower than $0.5 \times 10^9$/L was defined as day 1 and the first day the neutrophil count became more than $0.5 \times 10^9$/L, as the last day of neutropenia. The days of severe neutropenia with a neutrophil count of less than $0.1 \times 10^9$/L were defined by the same criteria.

*Definition of end points*

The end point was defined according to one of the following criteria (1) the first day the temperature increased to above 38.0°C, and (2) the day systemic antibiotics were initiated for suspected infection.

*Historical controls*

The medical records of all the patients with acute leukemia who were on polymyxin B, 1 million units, three times a day, between January 1989 and May 1990 were reviewed and pathogens isolated from blood cultures were analyzed.

*Statistical analysis*

Statistical analysis was conducted by using the SAS packages (SAS Institute, Inc., Cary, N.C.). Fisher's exact test was used to compare the differences in proportions between the two grousp. The one-tailed test was used to compare the effect of prognostic factors. The unpaired t-test was used to compare the means. The Mantel-Haenszel method for combination of two-by-two contingency tables was used to stratify patients retrospectively for prognostic factors. Logistic regression was used to assess the relative importance of the various prognostic factors. The Kaplan-Meier method and the generalized Wilcoxon test were used for time-to-event analysis.

## Results

*Patient characteristics*

A total of 141 neutropenic episodes in the 51 patients were included. In 76 episodes norfloxacin was used and in 65 episodes the drug was tosufloxacin, while 33 episodes were excluded from the analysis because neutropenia lasted less than 10 days (17 and 10 in the norfloxacin and tosufloxacin groups,

平成6年7月20日

Table 1 Patient characteristics according to treatment group

| Characteristic | Norfloxacin | Tosufloxacin | p |
|---|---|---|---|
| Neutropenia episodes, n | 55 | 53 | |
| Men/Women | 26/29 | 35/18 | 0.076 |
| Mean age (range), y | 42.95(15—66) | 42.04(16—67) | 0.750 |
| Underlying disease, n | | | |
| Acute lymphocytic leukemia | 12 | 12 | |
| Acute nonlymphocytic leukemia | 41 | 41 | |
| Non Hodgkin's lymphoma | 2 | 0 | 0.621 |
| Chemotherapy, n | | | |
| Induction | 19 | 16 | |
| Consolidation/Intensification | 36 | 32 | |
| Maintenance | 0 | 5 | 0.076 |
| LAF, n | 25 | 31 | 0.185 |
| TMP-SMX intake, n | 28 | 17 | 0.053 |
| Central venous catheter, n | 44 | 37 | 0.269 |
| Mean duration of neutropenia (range), d ($<0.5\times10^9$/L) | 19.16(10—64) | 17.83(10—39) | 0.413 |
| Mean duration of severe neutropenia (range), d ($<0.1\times10^9$/L) | 11.26 (0—26) | 11.43 (0—20) | 0.851 |

Table 2 Effects of prognostic factors

| Prognostic factor | Patients developing fever | Univariate P value | Logistic P value |
|---|---|---|---|
| Prophylactic regimen | n/N(%) | | |
| norfloxacin | 34/55(61.8) | 0.093 | 0.535 |
| tosufloxacin | 40/53(75.5) | | |
| Duration of neutropenia ($<0.5\times10^9$/L), d | | | |
| 10—15 | 29/49(59.2) | 0.045 | 0.088 |
| ≥16 | 45/59(76.3) | | |
| Duration of severe neutropenia ($<0.1\times10^9$/L), d | | | |
| <10 | 20/35(57.1) | 0.063 | 0.090 |
| ≥10 | 54/73(74.0) | | |
| LAF | | | |
| Yes | 45/57(78.9) | 0.012 | 0.088 |
| No | 29/51(56.9) | | |
| TMP-SMX intake | | | |
| Yes | 25/45(55.6) | 0.013 | 0.030 |
| No | 49/63(77.8) | | |
| Central vein catheter | | | |
| Yes | 55/81(67.9) | 0.506 | 0.614 |
| No | 19/27(70.4) | | |

Table 3 Effects of prophylactic regimen and prognostic factors on patient outcome

| Prognostic factor | Norfloxacin group n/N (%) | Tosufloxacin group n/N (%) | P value |
|---|---|---|---|
| Duration of neutropenia ($<0.5\times10^9$/L), d | | | |
| 10—15 | 15/27(55.6) | 14/22(63.6) | 0.391 |
| ≥16 | 19/28(67.9) | 26/31(83.9) | 0.128 |
| Duration of severe neutropenia ($<0.1\times10^9$/L), d | | | |
| <10 | 11/19(57.9) | 9/16(56.3) | 0.596 |
| ≥10 | 23/36(63.9) | 31/37(83.8) | 0.047 |
| LAF | | | |
| Yes | 17/26(65.4) | 28/31(90.3) | 0.040 |
| No | 17/29(58.6) | 12/22(54.6) | 0.551 |
| TMP-SMX intake | | | |
| Yes | 13/28(46.4) | 12/17(70.6) | 0.101 |
| No | 21/27(77.8) | 28/36(77.8) | 0.617 |
| Central vein catheter | | | |
| Yes | 26/44(59.1) | 29/37(78.4) | 0.052 |
| No | 8/11(72.7) | 11/16(68.8) | 0.586 |

respectively) and non-compliance with the protocol (4 and 2, respectively because they were found to have a diagnosis of other than acute leukemia and malignant lymphoma).

A total of 108 episodes were assessable, 55 episodes in the norfloxacin group and 53 in the tosufloxacin group. The two groups were similar in sex, age, underlying disease, type of chemotherapy received, duration and severity of neutropenia, and the use of an LAF system, TMP-SMX and central venous catheters. (Table 1)

*End point analysis*

In 13 episodes in patients receiving tosufloxacin, the patients did not develop a febrile episode, compared to 21 with over 55 episodes in the norfloxacin group. The mean durations of neutropenia in these

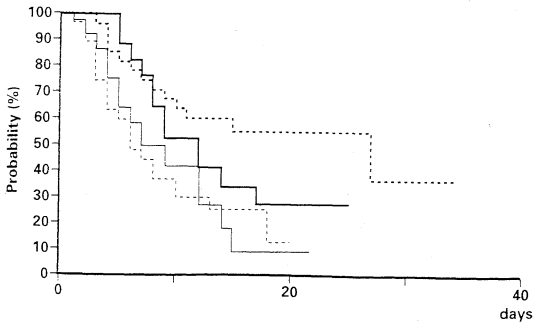


Fig. 1 Time-to-event analysis of end point.
(—), Tosulfoxacin without TMP-SMX; (—), tosufloxacin with TMP-SMX; (---), norfloxacin without TMP-SMX; (- - -), norfloxacin with TMP-SMX.

Table 4 Causative organisms identified in first febrile episode (%)

| Prophylactic regimen | Polymyxin B | Norfioxacin | Tosufioxacin |
|---|---|---|---|
| Episode | 55 | 55 | 53 |
| Gram-positive bacteria | 4 (7.3) | 5(9.1) | 6(11.3) |
| Streptococci | 1 | 2 | 2 |
| Staphylococci, coagulase-negative | 0 | 3 | 4 |
| Enterococci | 2 | 0 | 0 |
| Others | 1 | 0 | 0 |
| Gram-negative bacteria | 6(10.9) | 4(7.3) | 0 (0.0) |
| *Pseudomonas aeruginosa* | 2 | 4 | 0 |
| Others | 4 | 0 | 0 |

episodes were 15.2 days and 16.7 days, respectively. Univariate analysis of several prognostic variables revealed the duration of neutropenia, the use of TMP-SMX and the use of LAF to be predictive for the end point, but linear logistic regression analysis revealed only the use of TMP-SMX to be predictive ($p<0.05$). (Table 2)

To analyze the effect of treatment, patients were also stratified according to several prognostic factors. If the duration of severe neutropenia was prolonged or if the LAF system was used, norfloxacin seems to be more effective in preventing febrile episodes than tosufloxacin. Further subgroup analysis according to the use of TMP-SMX, however, revealed no statistically significant difference between the two treatment groups, suggesting that the differences observed were due to the use of TMP-SMX which decreased the incidence of febrile episodes and was used more frequently in the norfloxacin group. (Table 3)

Time-to-event analysis using the Kaplan-Meier method did not show any statistical difference between the norfloxacin group and the tosufloxacin group if they were compared according to the status of TMP-SMX use ($p<0.05$), but there was a significant difference if the episodes with and without TMP-SMX in each treatment group were compared ($p<0.05$). (Fig 1)

*Results of blood cultures*

The blood cultures obtained in the first febrile episode during neutropenia were positive on nine occasions in the norfloxacin group, with gram-positive bacteria obtained in five episodes and *Pseudomonas aeruginosa* in four, compared to six and none, respectively, in the tosufloxacin group. All gram-positive bacteria were coagulase-negative staphylococci or streptococci sensitive to broad spectrum antibiotics. (Table 4)

*Analysis of historical controls*

In 55 episodes of neutropenia observed in the patients receiving polymyxing B as a prophylactic between 1989 and May 1990, six episodes of gram-negative bacteremia and four of gram-positive bacteremia were observed, suggesting that quinolones are effective in preventing gram-negative bac-

teremia.

*Side effects*

Three patients in the tosufloxacin group developed skin eruptions which prevented further use of the medicine.

## Discussion

This was an open, non-randomized study comparing the efficacy of norfloxacin and tosufloxacin in preventing bacterial infection during neutropenic episodes after intensive chemotherapy in patients with hematological malignancies.

Norfloxacin had been shown to prevent bacteremia due to gram-negative bacteria except for *Pseudomonas*, but not that due to gram-positive bacteria, in neutropenic patietns[4)~7)].

Ciprofloxacin was then reported to be more active than norfloxacin in preventing febrile episodes, even though the incidence of gram-positive bacteremia remained the same[8)].

Tosufloxacin is another new quinolone which has broader activity against gram-positive bacteria than ciprofloxacin[9)]. The minimum inhibitory concentrations (MICs) of norfloxacin, ciprofloxacin, and tosufloxacin against *Staphylococcus aureus* (209P JC), for example, were 0.39, 0.39, and 0.05 μg/ml, respectively, and against *Streptococcus pyogenes* (Cook), 1.56, 0.78, and 0.10 μg/ml, respectively[9)]. Since tosufloxacin has the same or better antibacterial activity against gram-negative bacteria, it was expected to show the same or a better preventive effect against fever and gram-positive bacteremia in patients during the chemotherapy-induced neutropenia. However, the incidence of gram-positive bacteremia stayed the same in the two groups. Even though norfloxacin and tosufloxacin did decrease the incidence of gram-negative bacteremia compared to polymyxin B, and tosufloxacin was more effective in preventing the bacteremia due to *P. aeruginosa* than norfloxacin, the time-to-event analysis of the end points or the incidence of non-febrile episodes did not support the expected difference between norfloxacin and tosufloxacin, either.

This might be due to the small number of episodes in this study or to the non-randomized study design. The incidence of bacteremia due to *P. aeruginosa*, however, was shown to be decreased by tosufloxacin.

The MICs of norfloxacin, ciprofloxacin, and tosufloxacin against *P. aeruginosa* (E-2) have been reported to be 1.56, 0.78, and 0.20 μg/ml, respectively[9)]. The MIC of tosufloxacin for *Pseudomonas*, against which tosufloxacin was effective, was eight times lower than that of norfloxacin, while it was 8 to 10 times lower for streptococci and staphylococci without any beneficial effect, even though the absolute level of MIC was much higher for *P. aerugonosa*.

This suggests the possibility that gram-positive bacteria invade through sites such as skin, oral mucosa, or venous routes, rather than through the gastrointestinal tract. To decrease the incidence of gram-positive bacteremia, therefore, it might be reasonable to develop a technique to prevent infection through an intravenous port and to maintain better oral hygiene rather than using stronger medication to suppress gram-positive bacteria in the gastrointestinal tract. The finding that oral vancomycin failed to suppress gram-positive septicemia also seems to support this speculation[10)].

If we strengthen the prophylactic regimen further to suppress gram-positive bacteria, we may also select multi-drug resistant bacteria, especially enterococci, to colonize the gastrointestinal tract. Actually, surveillance cultures of the stool revealed colonization by resistant enterococci in at least 30% of the patients who are receiving quinolones in our institution[11)]. With increasing numbers of reports on vancomycin-resistant enterococci published recently, the fact that this bacterium remained in the gastrointestinal tract of neutropenic patients is a matter of concern[12)].

In this study, the use of TMP-SMX turned out to be a predictive factor in each group. Although this study was performed without randomization and the use of TMP-SMX depended upon the diagnosis, this

result suggests an at least possible synergistic effect of TMP-SMX and quinolones in preventing febrile episodes in the patient with neutropenia.

Further evaluation of other methods of prophylaxis in neutropenic patients is therefore warranted.

*Acknowledgment* We thank Ms K. Nakamura for the preparation of this manuscript.

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平成6年7月20日

# 血液疾患の化学療法による顆粒球減少におけるノルフロキサシンとトスフロキサシンの細菌感染の予防効果

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(平成6年2月8日受付)
(平成6年4月6日受理)

## 要 旨

血液悪性疾患の化学療法後の細菌感染に対する，ニューキノロン系抗菌剤の予防的投与の効果を検討した．1990年5月より1992年9月までに，当科へ入院した急性白血病及び悪性リンパ腫の51症例を対象に化学療法開始と共に経口抗生物質の予防的投与を開始し，好中球数が500/μl以上に回復するまで継続投与した．経口抗生物質としては，1991年10月までnorfloxacin（NFLX）600mg/日を使用し，1991年11月以降はtosufloxacin (TFLX) 600mg/日の投与に変更した．化学療法施行後，10日以上継続する好中球減少時における発熱の頻度と時期，菌血症の原因菌等を2群間で比較し検討した．

予防投与は51症例で計141回行われ，NFLX群では55回，TFLX群では53回が解析対象となった．発熱はNFLX群では34/55，TFLX群では40/53に認められ，発熱の頻度と時期において，両群に差は認められなかった．

予防投与中の発熱時に採取された血液培養より，NFLX群ではグラム陰性菌，陽性菌が各4および5例に，TFLX群では0，6例に認められた．1990年以前の顆粒球減少期にpolymyxin Bを予防投与された白血病患者に認められた菌血症の原因菌と比較し，グラム陰性菌による菌血症の頻度は低下し，緑膿菌菌血症はTFLXにより最も抑制された．

また，sulfamethoxazole-trimethoprimにより両群に発熱頻度の低下を認め，同薬剤による相乗効果の可能性が示唆された．