An Optimal Approach for Fluoroquinolone Garenoxacin Prophylaxis in Patients with Hematological Malignancies and Chemotherapy-induced Neutropenia

Mushino T1*, Hanaoka N1,2*, Murata S1, Kuriyama K1, Hosoi H1, Nishikawa A1, Tamura S1, Nakakuma H1,2 and Sonoki T1

1Department of Hematology/Oncology, Wakayama Medical University, Wakayama, Japan
2Department of Internal Medicine, Kagoshima Tokushukai Hospital, Kagoshima, Japan

Abstract

Antibiotic prophylaxis such as that with fluoroquinolone reportedly reduces infectious episodes in patients receiving chemotherapy regimens with the risk of febrile neutropenia. However, optimum patient characteristics, the timing of initiation, and antibiotics for prophylactic treatments have yet to be identified. We herein conducted a single-arm monocenter clinical study to elucidate the therapeutic profiles of fluoroquinolone garenoxacin prophylaxis for patients with hematological malignancies (HMs). Fever was not present for the duration of chemotherapy-induced neutropenia in 29 (43.9%) out of 66 patients. A shorter duration of prophylaxis until chemotherapy-induced neutropenia had a more potent effect on delaying febrile episodes, even in patients with fever. Excessive neutropenia (minimum zero neutrophils/l) negatively affected prophylactic effects. Garenoxacin accounted for 4.5% of the minor adverse events observed such as mild renal damage and skin reactions. Therefore, the study suggests that the initiation of garenoxacin prophylaxis from the introduction of neutropenia could be an effectual strategy for preventing chemotherapy-induced febrile episodes in HM patients with moderate neutropenia.

Keywords: Prophylaxis; Fluoroquinolone; Garenoxacin; Febrile Neutropenia; Hematological Malignancies

Introduction

Chemotherapy-induced neutropenia allows bacterial infections to develop into severe systemic infections, resulting in interruptions in chemotherapy treatments with a higher risk of cancer relapse and mortality [1-3]. Therefore, the prevention and control of infection is crucial for the successful treatment of patients with hematological malignancies (HMs). The advent of new anti-infective drugs has led to improvements in intractable infectious complications [4,5], but not to reductions in the frequency of infections [6,7]. Then, we found that infection rates were significantly lower in cancer patients prophylactically treated with antibiotics such as trimethoprim-sulfamethoxazole and oral quinolones than in placebo recipients [8,9]. However, routine antibiotic prophylaxis is not recommended for all patients with anticipated prolonged and severe neutropenia due to some associated disadvantages including drug-related adverse reactions, increased medical expenses, and the development of antibiotic resistance [8,10,11]. In current practice guidelines by the Infectious Diseases Society of America (IDSA) and National Comprehensive Cancer Network (NCCN), B-I and category 2A prophylaxis, respectively, is recommended for limited patients undergoing chemotherapy with anticipated <0.1×109 neutrophils/l lasting more than 7 days. Thus, optimum patient characteristics, the timing of initiation, and antibiotics, which may be used as prophylactic treatments, have yet to be identified.

Garenoxacin, a novel des-F (6)-quinolone, has only been approved in Japan. It exhibits activity against a wider range of organisms including traditional quinolone-resistant strains and is mainly excreted in bile [12-14], which suggests drug-favorable access to the intestines permitting chemotherapy-induced bacterial translocation.

We herein elucidated the therapeutic profiles of prophylaxis with garenoxacin in patients with HMs and chemotherapy-induced neutropenia and also considered a realistic strategy against prophylaxis with fluoroquinolone including garenoxacin for practical physicians.

Patients and Methods

Patients

Ninety-five adult patients with HMs such as leukemia, malignant lymphoma, and myeloma between June 2011 and April 2013 in our institute participated in the present study. Patient enrollment is shown in Figure 1. The characteristics of 66 patients (32 men and 34 women;
mean age 54 (range, 19-77) years whose responses to therapy were assessable are provided in Table 1.

**Study design**

The present study was designed as a single-arm, monocenter study and was approved by the Institutional Review Board at Wakayama Medical University. The study procedures conformed to the Helsinki Declaration, and informed consent was obtained from all patients. Patients with neutropenia (<1.0 × 10^9/L) lasting more than 7 days received garenoxacin (400 mg daily) until neutrophil numbers recovered in accordance with a levofloxacin study [8]. Patients were examined daily for the clinical signs of infection including axillary temperature. We defined a fever event as exceeding 38.5°C once or 38°C at least twice during a period of 12 h [8]. When an infection was suspected, blood specimens and cultures of infection-suspected sites were obtained for microbiological cultures and empirical antibacterial therapy with broad-spectrum antibiotics was intravenously initiated. Granulocyte colony-stimulating factors were prescribed empirically at the typical doses for limited patients with lymphoid malignancies and undergoing stem cell transplantation. Medical staff ensured proper medication adherence.

**Statistical analysis**

Fever-free survival was estimated using the Kaplan-Meier method. The Mann-Whitney U test was used to determine significance levels when comparing two groups. Febrile episodes due to differences in neutrophil and leukocyte counts were compared by the chi-squared test. P values less than 0.05 were considered significant.

**Results**

The mean duration of the treatment with garenoxacin was 24.7 (range, 11-56) days (Table 1). Of the 66 patients with HMs and chemotherapy-induced neutropenia who received prophylactic garenoxacin, 29 (43.9%) remained afebrile until neutrophil numbers recovered (Figure 2 and Table 1). The median duration of febrile neutropenia was 6 (range, 1-44) days while the mean durations of neutropenia and hospitalization were 16.4 (range, 7-47) and 33.8 (range, 15-179) days, respectively (Table 1). When examined more closely, patients receiving garenoxacin prophylaxis with excessive neutropenia (zero neutrophils) were virtually febrile (Table 2). The incidence of chemotherapy-associated neutropenic fever was significantly lower (77.8% to 22.2%; p<0.05) in patients receiving garenoxacin prophylaxis whose leukocytes decreased to between 0.5 and 1×10^9/L (Table 2). In addition, a shorter duration of prophylaxis until chemotherapy-induced neutropenia had a more potent effect on delaying febrile episodes, even in patients with fever (Figure 3). On the basis of the 2010 Infectious Diseases Society of America guidelines, no significant differences were observed in the endpoint incidence of febrile neutropenia between the high and low risk groups; 7 out of 13 patients (53.8%) and 30 out of 53 patients (56.6%), respectively (Table 2). No infection-related death occurred in any of the patients who participated in this study. Of note, the incidence of fluoroquinolone-resistant stain showed a slight decrease while the prophylactic use of levofloxacin, which had been prevailed in our unit, was avoided during the present study (Figure 4). There were 6 cases of bacteremia (9.1%) due to methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis*, and 4 Gram-negative bacilli. Eighty-three percent of these receiving garenoxacin prophylaxis were resistant to fluoroquinolone (5 of 6). Three adverse events were observed that were
Table 1: Minimum counts of neutrophils and leukocytes
grouped by risk of infections (n=66).

| Risk groups | Minimum neutrophil count (x10^9/L) | Febrile | Afebrile | p |
|-------------|------------------------------------|---------|---------|---|
| Very high   | ≤0.1                               | 23      | 72%     | 9 28% | <0.05 |
|             | 0.1-0.2                            | 5       | 71%     | 2 29% |
|             | 0.2-0.3                            | 3       | 38%     | 5 62% |
|             | 0.3-0.4                            | 3       | 50%     | 3 50% |
|             | 0.4-0.5                            | 1       | 25%     | 3 75% |
|             | 0.5%                               | 2       | 22%     | 7 78% | <0.05 |
| Intermediate|                                    |         |         |     | |
| Low         |                                    |         |         |     | |

Table 2: Febrile episodes involved in neutrophil and leukocyte counts and risk groups. Very high risk includes patients undergoing autologous hematopoietic stem cell transplantation (HSCT); high risk includes patients receiving remission induction chemotherapy; intermediate risk includes patients receiving consolidation chemotherapy and autologous HSCT; low risk includes patients with lymphoma receiving salvage chemotherapy.

Discussion

Garenoxacin prophylaxis was tolerated well and fever developed in 56.1% of patients receiving prophylaxis in the present study. Among the risk classifications, no significant differences in patient outcomes were observed in the neutrophil counts of patients. On the other hand, a previous study reported that 85% of patients with no antibacterial prophylaxis presented with fever during neutropenia [8]. Based on the present results and these findings, garenoxacin appears to be an antibiotic candidate that may be prophylactically used for fever prevention in a similar manner to levofloxacin. Garenoxacin has only been clinically used and studied in Japan [15] and will be readily available globally. The monocenter single-arm design of the present study also permitted the assessment of patient selection bias in the prophylactic treatment. A randomized-control trial to examine the potential of preventing fever through the prophylactic use of garenoxacin is warranted.

Patients with excessively severe neutropenia (a nadir neutrophil of zero per cubic millimeter) were significantly febrile regardless of prophylaxis in the present study. This result, in contrast to the recommendations of influential practice guidelines, suggests that the prompt administration of an empirical antibiotic or prophylaxis with another fluoroquinolone instead of garenoxacin may result in a good outcome for these patients. Therefore, it is conceivable that neutrophils assume a vital role in reducing infection and enhancing antibiotic effects.

On the other hand, a prolonged and single exposure to antibiotics often permits the outbreak of antibiotic-resistant organisms [8-11,16]. A total of 9.1% of patients receiving the prophylactic garenoxacin had microbiologically documented bacteremia in the present study. Of these, 4.5% had Gram-negative bacilli while 3.0% had Gram-positive cocci. Each total of 4% and 11% of patients receiving prophylactic levofloxacin, which we had exclusively used prior to this study, had Gram-negative bacilli and Gram-positive cocci, respectively [8], which appears to be in part attributable to the novel agent garenoxacin exhibiting higher activity against Gram-positive strains. Clinically documented infections were virtually all fluoroquinolone-resistant organisms. Fluoroquinolone resistance showed a potentially reversible phenomenon after the avoidance of levofloxacin prophylaxis in our study, thereby supporting the efficacy of prophylactic fluoroquinolone heterogeneity for preventing the outbreak of antibiotic resistance [16].

The optimal use of antibiotic prophylaxis would be proposed on the basis of this study in which fluoroquinolones including garenoxacin are prophylactically administered to HM patients from a decline in neutrophils, allowing heterogeneous antibiotic use along with levofloxacin for the prevention of fluoroquinolone resistance in prophylaxis. Indeed, when focusing simply on the timing of fluoroquinolone prophylaxis in published studies [9], the patients starting fluoroquinolone prophylaxis from a decline in neutrophils...
often have a low incidence of febrile neutropenia. In addition, it may be better to stop prophylaxis after a zero neutrophil count or the recovery of neutrophil numbers in order to achieve a more streamlined process and cost savings. An assessment of clinical outcomes in a large global population trial is required.

Therefore, the results of the present study provide an insight into the potency of garenoxacin for prophylaxis, and may influence the successful treatment of HM patients with chemotherapy-induced moderate neutropenia.

Author Contributions
TM and NH designed and performed the research, analyzed the data, and wrote the manuscript. SM, K.K, HH, AN and ST analyzed the clinical data. HN and TS supervised the project.

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Conflict of Interest Statement
No conflicts of interest are declared.

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References
1. Pizzo PA, Thaler M, Hathorn J, Hiemenez J, Skelton J, et al. (1985) New beta-lactam antibiotics in granulocytopenic patients. New options and new questions. Am J Med 79: 75-82.
2. Gonzalez-Barca E, Fernandez-Sevilla A, Carratala J, Salar A, Peris J, et al. (1999) Prognostic factors influencing mortality in cancer patients with neutropenia and bacteremia. Eur J Clin Microbiol Infect Dis 18: 539-544.
3. Whimbey E, Kiehn TE, Brannon P, Blevins A, Armstrong D (1987) Bacteremia and fungemia in patients with neoplastic disease. Am J Med 82: 723-730.
4. Dowell SF, Kupronis BA, Zell ER, Shay DK (2000) Mortality from pneumonia in children in the United States, 1939 through 1996. N Engl J Med 342: 1399-1407.
5. Bodey GP, Rodriguez V, Chang HY, Narboni (1978) Fever and infection in leukemic patients: a study of 494 consecutive patients. Cancer 41: 1610-1622.
6. Lepage E, Gisselbrecht C, Haïoun C, Sebban C, Tilly H, et al. (1993) Prognostic significance of received relative dose intensity in non-Hodgkin’s lymphoma patients: application to LNH-87 protocol. The GELA. (Groupe d’Etude des Lymphomes de l’Adulte). Ann Oncol 4: 651-656.
7. Bosly A, Bron D, Van Hoof A, De Bock R, Berneman Z, et al. (2008) Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. Ann Hematol 87: 277-283.
8. Bucaneve G, Micoczi A, Menichetti F, Martino P, Dionisi MS, et al. (2005) Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 353: 977-987.
9. Gaffter-Gvili A, Fraser A, Paul M, Leibovici L (2005) Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 142: 979-995.
10. Horvathova Z, Spanik S, Sufliarsky J, Mardiak J, Pichna P, et al. (1998) Bacteremia due to methicillin-resistant staphylococci occurs more frequently in neutropenic patients who received antimicrobial prophylaxis and is associated with higher mortality in comparison to methicillin-sensitive bacteremia. Int J Antimicrob Agents 10: 55-58.
11. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, et al. (2002) 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 34: 730-751.
12. Takahata M, Mitsuyama J, Yamashiro Y, Yonezawa M, Araki H, et al. (1999) In vitro and in vivo antimicrobial activities of T-3811ME, a novel des-F(6)-quinolone. Antimicrob Agents Chemother 43: 1077-1084.
13. Fung-Tomc JC, Nasrallah L, Hladik B, Ebert E, Aleksunes L, et al. (2000) Antibacterial spectrum of a novel des-fluoro(6) quinolone, BMS-284756. Antimicrob Agents Chemother 44: 3351-3356.
14. Nord CE, Gajar DA, Grasela DM (2002) Ecological impact of the des-F(6)-quinolone, BMS-284756, on the normal intestinal microflora. Clin Microbiol Infect 8: 229-239.
15. Uni M, Yoshimi A, Yamazaki S, Taoka K, Shinohara A, et al. (2015) Comparison of garenoxacin with levofloxacin as antimicrobial prophylaxis in acute myeloid leukemia. Jpn J Clin Oncol 45: 745-748.
16. Murata S, Mushino T, Hosoi H, Kuriyama K, Kurimoto M, et al. (2015) Real-time monitoring of antimicrobial use density to reduce antimicrobial resistance by promoting the promotion of antimicrobial heterogeneity in a haematology/oncology unit. J Antimicrob Chemother 70: 2681-2684.