

Original Article

Efficacy of oral levofloxacin monotherapy against low-risk FN in patients with malignant lymphoma who received chemotherapy using the CHOP regimen

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The safety and feasibility of oral fluoroquinolone monotherapy in patients with low-risk febrile neutropenia (FN) were demonstrated in recent studies. Levofloxacin (LVFX) is a commonly prescribed antibiotic; however, evidence for its efficacy against FN is limited. Therefore, in this study, we retrospectively investigated the efficacy of LVFX against low-risk FN in patients with malignant lymphoma at our institution. Treatment success was defined as recovery from fever and neutropenia without alteration of the initial regimen. We recruited 29 patients between January 2013 and December 2018. The median age of the cohort was 64 (range: 21–87) years; 13 (44.8%) were aged over 65 years. In total, 22 patients had diffuse large B-cell lymphoma (DLBCL). Therapy was successful in 24 (82.8%) patients, whereas 5 had treatment failure requiring a change from LVFX to intravenous broad-spectrum antibacterial agents. No deaths related to FN were observed. Two patients required FN-related chemotherapy dose reduction in subsequent cycles. Although this cohort comprised many elderly patients, our study confirmed the efficacy of LVFX in patients with low-risk FN. This may improve the treatment of low-risk FN and malignant lymphoma.

Keywords: febrile neutropenia, levofloxacin, malignant lymphoma, CHOP

INTRODUCTION

Combination chemotherapy using cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) is the standard treatment regimen for malignant lymphoma.¹⁻³ CHOP-induced neutropenia is a common clinical complication that often develops into life-threatening febrile neutropenia (FN). This may necessitate treatment interruptions and delays, which reduce the administered doses of chemotherapy, significantly deteriorating survival outcomes and the quality of life.⁴⁻⁶ Therefore, the prompt initiation of intravenous broad-spectrum antibiotics is necessary in such cases.⁷

However, a subset of FN patients with a low risk for medical complications was identified. Controlled trials comparing oral and intravenous antibiotics in patients with low-risk FN reported equivalence in terms of safety and efficacy.⁸ Several guidelines recommend oral ciprofloxacin as initial empiric therapy with amoxicillin/clavulanate for low-risk FN.^{7,9}

Recent studies demonstrated the safety and feasibility of oral fluoroquinolones in patients with low-risk FN.^{10,11} Levofloxacin (LVFX) is a commonly prescribed fluoroquinolone antibiotic;¹² however, evidence for its efficacy is limited. We therefore retrospectively investigated the efficacy of oral LVFX monotherapy in against low-risk FN in patients with malignant lymphoma who received chemotherapy using the CHOP regimen at our institution.

MATERIALS AND METHODS

Study design

This was a single-center retrospective study and the protocol was approved by the institutional review board of the Fukuoka University Hospital. As it was based exclusively on existing data from medical records, the requirement for informed consent was waived.

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Patients

We reviewed the medical records of patients with malignant lymphoma who received CHOP therapy between January 2013 and December 2018 at the Fukuoka University Hospital. The data of patients who developed FN and were treated using 500 mg of LVFX orally per day were extracted. Patients received LVFX for at least 5 days if they did not need to change from LVFX to another antibiotic. In patients who received LVFX more than once, the second and subsequent treatments were excluded from analysis.

Assessments

The data obtained from the records included the age, sex, Eastern Cooperative Oncology Group Performance status (ECOG PS), lymphoma subtype, rituximab administration, complications (heart failure, chronic obstructive pulmonary disease [COPD], and cerebral hemorrhage/infarction), infection, prophylactic interventions (antibiotics and granulocyte-colony stimulating factor; G-CSF), magnesium oxide administration, previous LVFX administration within 3 months, previous hospitalization within 3 months, blood tests, fever duration, and outcomes of therapy.

Definitions

FN is defined as an axillary temperature of $\geq 37.5^{\circ}\text{C}$ and an absolute neutrophil count of < 500 cells/ mm^3 or that is expected to decrease to < 500 cells/ mm^3 during the next 48 h. Low-risk patients were identified based on a Multinational Association of Supportive Care in Cancer (MASCC) risk-index score of ≥ 21 .¹³ The predictive factors were: a burden of illness suggesting the absence of symptoms or mild symptoms (weight, 5) or moderate symptoms (weight, 3); absence of hypotension (weight, 5); absence of chronic obstructive pulmonary disease (weight, 4); presence of solid tumor or absence of previous fungal infection in patients with hematological malignancies (weight, 4); outpatient status (weight, 3); absence of dehydration (weight, 3); and age less than 60 years (weight, 2).

Treatment success was defined as recovery from fever and neutropenia without alteration of the initial regimen, i.e., LVFX.

In cases where a pathogen was isolated from a blood sample, an infection site, or both, the infection was considered to be microbiologically documented. In cases of clinical signs and symptoms of infection without isolation of pathogens from the infection site, the infection was considered to be clinically documented. Fever of unknown origin was diagnosed in cases where fever was the only clinical sign of infection.

RESULTS

Patients

In total, 182 patients received CHOP therapy for malignant lymphoma. FN developed in 60 (33.0%) patients in 80

(8.6%) of 933 cycles of CHOP therapy administered in total. We assessed only the first FN event for each patient in the following analysis. Eighteen (30.0%) patients had high-risk FN and received intravenous antibiotics on admission. Thirty-five (58.3%) patients had low-risk FN, among whom 29 required oral LVFX, 4 required intravenous broad-spectrum antibacterial therapy, and 2 required oral antibiotics other than LVFX (ciprofloxacin plus amoxicillin/clavulanate and ciprofloxacin alone). The MASCC score was undetermined in 7 (11.7%) patients.

The characteristics of the 29 patients at the start of CHOP therapy are shown in Table 1. The median age was 64 (range: 21–87) years and 13 (44.8%) patients were aged over 65 years. The ECOG PS was 0-1 in 27 patients and 2 in 2. The subtype of lymphoma was diffuse large B-cell lymphoma (DLBCL) in 22, follicular lymphoma in 3, Adult-T cell leukemia/lymphoma in 2, and peripheral T-cell lymphoma not otherwise specified in 2. A total of 24 patients received rituximab. None of the patients had a medical history of heart failure, COPD, or cerebral hemorrhage/infarction. We did not evaluate whether our patients were positive for HIV.

Clinical features of FN

We next investigated the clinical features of the 29 patients when they developed FN. Twenty-eight (96.6%) patients had an ECOG PS of 1 and 1 had an ECOG PS of 2 (Table 2). No patient had non-hematological toxicity, including renal and hepatic function of at least Common Terminology Criteria for Adverse Events grade 1. Five

Table 1. Baseline patient characteristics (n=29)

Characteristics	No. (%)
Age, years	
Median (range)	64 (21-87)
Sex	
Male	13 (44.8)
Female	16 (55.2)
ECOG PS	
0-1	27 (93.1)
2	2 (6.9)
Malignancy	
DLBCL	22 (75.9)
FL	3 (10.3)
ATLL	2 (6.9)
PTCL-NOS	2 (6.9)
Rituximab	24 (82.8)
Comorbidity	
Heart failure	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)
Cerebral hemorrhage/infarction	0 (0.0)

ECOG PS: Eastern Cooperative Oncology Group Performance Status, DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma, ATLL: adult-T-cell leukemia/lymphoma, PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified

Table 2. Clinical features of 29 patients with FN (n=29)

Characteristics	No. (%)
ECOG PS	
1	28 (96.6)
2	1 (3.4)
Type of infection	
Microbiologically documented	0 (0.0)
Clinically documented	5 (17.2)
Fever of unknown origin	24 (82.8)
Prophylactic antibiotics	0 (0.0)
Prophylactic G-CSF	13 (44.8)
Magnesium oxide	18 (62.1)
Previous LVFX within 3 months	3 (10.3)
Previous hospitalization within 3 months	18 (62.1)
Blood parameters (median)	
White blood cells	0.80×10 ⁹ /L
Neutrophils	0.26×10 ⁹ /L
Hemoglobin	10.6 g/dL
Platelets	130×10 ⁹ /L
Albumin	3.6 g/dL
Creatinine	0.8 mg/dL
Total bilirubin	0.7 mg/dL
Aspartate aminotransferase	21 U/L
Alanine aminotransferase	25 U/L
Lactate dehydrogenase	178 U/L
Glucose	112 mg/dL
C-reactive protein	0.8 mg/dL

ECOG PS: Eastern Cooperative Oncology Group Performance Status, G-CSF: granulocyte-colony stimulating factor, LVFX: levofloxacin

patients (17.2%) were diagnosed with clinical documented infection, among whom 3 had gingivitis and 2 had pharyngitis. G-CSF was administered for FN prophylaxis to 13 (44.8%) patients. Magnesium oxide was administered as a laxative to 18 (62.1%) patients. Three (10.3%) patients had a history of LVFX administration and 18 (62.1%) had been hospitalized within 3 months.

Outcomes of FN therapy

FN was improved by oral LVFX treatment in 24 (82.8%) patients (Table 3). Seventeen of 24 patients became afebrile within 72 hours and 3 patients in whom fever persisted for longer than 72 hours continued to receive oral LVFX because their conditions were clinically stable, leading to normalization of their body temperature with neutrophil recovery. In four patients with treatment success, we were unable to follow the fever duration. The remaining 5 (17.2%) patients changed from LVFX to intravenous broad-spectrum antibacterial therapy because 1 developed new signs and symptoms of infection, 1 became hemodynamically unstable, and 3 had persistent fever. Following the alteration of antibacterial therapy, all 5 patients recovered from fever and neutropenia. No patient discontinued LVFX due to side effects and no FN-related death was observed in this cohort.

Table 3. Treatment and outcomes (n=29)

Characteristics	No. (%)
Outcome of therapy	
Success	24 (82.8)
Failure	5 (17.2)
Death	0 (0.0)
Fever duration in successfully treated patients	
≤72 hours	17 (70.8)
>72 hours	3 (12.5)
Unknown	4 (16.2)
Subsequent cycles	
Dose reduction	2 (6.9)

Although treatment for FN was successful, 2 patients required FN-related chemotherapy dose reduction in the subsequent cycles. In 1 patient, the dose reduction was based on the criteria of clinical trials, whereas the other patient was 87 years old and required dose reduction due to PS deterioration.

DISCUSSION

In this study, LVFX therapy was successful in 82.8% of the patients with malignant lymphoma who developed low-risk FN following CHOP therapy. The use of oral monotherapy with fluoroquinolones has been investigated for low-risk FN. Prior studies demonstrated equivalent efficacy between moxifloxacin and oral ciprofloxacin with amoxicillin/clavulanate,¹⁰ and ceftriaxone in patients with low-risk FN.¹¹ Furthermore, ofloxacin and gatifloxacin were previously reported to be effective in patients with FN.¹⁴⁻¹⁶ LVFX is one of the most frequently prescribed antibiotics. Cornely *et al.* evaluated the efficacy of once-daily oral LVFX in comparison with intravenous piperacillin/tazobactam 3 times a day for 34 patients with low risk-FN following chemotherapy in a prospective, randomized, controlled multicenter trial.¹⁷ Although the planned number of patients was not enrolled, resulting in premature cessation of the trial, they demonstrated LVFX treatment to be successful in 13/17 (76.5%) of FN cases after 72 hours of treatment and found it to have equivalent efficacy to piperacillin/tazobactam. Lixian *et al.* also reported LVFX to be effective in 97.6% of patients with low-risk FN 7 days after the initiation of therapy in a pilot study.¹⁸ Thus, LVFX may be effective in patients with low-risk FN and our findings are consistent with those of previous studies.

Of note, our cohort had 13 (44.8%) patients aged 65 or older and the median age was 64 years. Thirteen patients aged over 65 years received CHOP therapy at a median dose of 100% (75-100%) when they developed FN and the median number of cycles of CHOP therapy was 6 (2-8). Among them, FN was successfully treated in 11 (84.6%).

Older age was found to be one of the risk factors for the development of complications in patients with FN by the MASCC risk index.¹³ Gómez H *et al.* reported infections to be the most common cause for chemotherapy-related

mortality in elderly patients with aggressive non-Hodgkin's lymphoma,¹⁹ and infection was the cause of death in 29/35 (82.9%) patients. Therefore, further studies are needed to establish the optimal treatment approach in elderly patients with FN.

However, the evidence for the efficacy of antibiotics in elderly patients with FN is limited. Yasuda *et al.* evaluated the efficacy of CFPM in patients with FN whose median age was 61 in a randomized controlled trial, and efficacy was noted in 19/25 (76.0%).²⁰ Regarding oral fluoroquinolone monotherapy, Chamilos *et al.* demonstrated that moxifloxacin was effective for 50/55 (91%) outpatients with a median age of 62 years.²¹ However, many other reports describing the efficacy of oral single-agent broad-spectrum fluoroquinolones in patients with low-risk FN were of studies on children^{16,22,23} or on adults with median ages of 40-50;^{10,11,14,15,20,24} our adult patient cohort was older by 10 years.

Previous reports suggested that a poor PS (2-4) is also an important poor prognostic factor for chemotherapy-related mortality.¹⁹ However, in our study, almost all (96.6%) patients had a PS of 1 when they developed FN. Furthermore, the presence of comorbidities is also known to be an independent risk factor for a poorer OS in patients with DLBCL treated using rituximab-CHOP.²⁵ In this study, we evaluated the presence of heart failure, cerebral infarction/hemorrhage, and COPD based on the Charlson comorbidity index,²⁶ which is an indicator of comorbidity. However, the patients in our cohort did not have these diseases. Therefore, if selected appropriately, LVFX is effective in patients with low-risk FN, irrespective of age.

LVFX is a concentration-dependent antibacterial drug; therefore, it is important to attain a high C_{max} for therapeutic effects. However, concurrent administration of antacids, including magnesium and aluminum compounds, is known to reduce the bioavailability of LVFX by 15-52%.²⁷ As such, pharmacists usually instruct patients not to take magnesium within a 2-hour period before or after LVFX administration. In our study, 62.1% of patients were receiving magnesium as a laxative when they developed FN. Satisfactory therapeutic effects were noted in this cohort despite this factor.

This study had several limitations. It was a retrospective cohort study performed at a single institution and there were few events. We also non-uniformly recruited patients with both B-cell and T-cell lymphoma undergoing CHOP therapy with or without rituximab.

In conclusion, our study suggests that oral LVFX is effective for treating patients with low-risk FN. This may improve the treatment of low-risk FN and malignant lymphoma. However, careful consideration is required for elderly patients. Further prospective studies on larger cohorts are needed to confirm our findings.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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