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MAJOR ARTICLE

Levofloxacin to Prevent Bacterial Infection in Patients With Acute Myeloid Leukemia Treated by Venetoclax and Azacitidine: A Toulouse-Bordeaux DATAML Registry Study

Xavier Brousse,[1,a] Nicolas Rasandisona,[2,a] Emilie Bérard,[3] Harmony Leroy,[1] Karen Delavigne,[4] Nathan Mottal,[1] Suzanne Tavitian,[5] Thibaut Leguay,[1] Léopoldine Lapierre,[5] Eric Delabesse,[6] Audrey Bidet,[7] Martin Gauthier,[8] Diane Lara,[9] Anne Banos,[10] Jennifer Guiraud,[11] Pauline Floch,[12] Leila Ghenim,[13] Audrey Sarry,[5] Anne-Charlotte de Grande,[1] Clémentine Béranger,[1] Christian Récher,[5] Arnaud Pigneux,[1] Sarah Bertoli,[5] and Pierre-Yves Dumas[1]

[1]CHU Bordeaux, Service d'Hématologie Clinique et de Thérapie Cellulaire, Bordeaux, France, [2]Service des Maladies infectieuses et tropicales, Toulouse University Hospital, Toulouse, France, [3]Centre Hospitalier Universitaire de Toulouse, Service d'Epidémiologie, CERPOP, Inserm, Université Toulouse III Paul Sabatier, Toulouse, France, [4]Service de Médecine Interne, Toulouse University Hospital, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France, [5]Service d'Hématologie, Toulouse University Hospital, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France, [6]Laboratoire d'Hématologie Biologique, Toulouse University Hospital, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France, [7]CHU Bordeaux, Laboratoire d'Hématologie Biologique, Bordeaux, France, [8]Service d'Hématologie, Cahors Hospital, Cahors, France, [9]Service d'Hématologie, Robert Boulin Hospital, Libourne, France, [10]Service d'Hématologie, Côte Basque Hospital, Bayonne, France, [11]CHU Bordeaux, Laboratoire de Bactériologie, Bordeaux, France, [12]Laboratoire de Bactériologie-Hygiène, Centre Hospitalier Universitaire de Toulouse, Toulouse, France, and [13]Service d'Hématologie, Rodez Hospital, Rodez, France

Objectives. Antibiotic prophylaxis for patients with cancer remains a controversial issue and is not broadly recommended for hematological malignancies. The venetoclax (VEN) and azacitidine (AZA) combination allows for high rates of complete remission in acute myeloid leukemia (AML) but enhances the incidence of febrile neutropenia (FN) compared to AZA alone, making primary antibiotic prophylaxis a relevant question.

Patients and Methods. Patients with AML who received VEN-AZA were selected from the DATAML registry to investigate the use of levofloxacin (LEVO) prophylaxis, administered at 500 mg/day from day 10 following the first course of VEN-AZA, until neutrophil recovery ($>0.5 \times 10^9$/L).

Results. A cohort of 258 patients was identified (median age 69.8 years, interquartile range 20.4–87.4), with 72 having received LEVO and 186 treated with standard of care (SOC). VEN-AZA was used for newly diagnosed AML in 52.7% of cases. FN occurred in 33.3% of LEVO patients versus 37.1% of SOC patients ($P = .572$). Time from day 10 VEN-AZA to FN was significantly delayed in LEVO patients (12.5 days vs 8 in SOC; $P = .037$). Pulmonary infections were considerably reduced by LEVO (10.2% vs 1.4%, $P = .018$) as well as those involving Enterobacterales (9.1% vs 1.4%; $P = .029$). No early increase in fluoroquinolone resistance was detected ($P = .142$).

Conclusions. Levofloxacin as primary prophylaxis in patients with AML treated with VEN-AZA seems to decrease the rate of documented infections even if the incidence of FN was not significantly decreased. This prophylaxis shaped a different clinical and microbiological landscape without significant increase of antibiotic resistance.

Keywords. acute myeloid leukemia; azacitidine; febrile neutropenia; levofloxacin; venetoclax.

The benefit of intensive front-line chemotherapy for acute myeloid leukemia (AML) is mitigated for elderly and unfit patients. The backbone treatment of these patients has been recently modified since the azacitidine (AZA)-venetoclax (VEN) association was demonstrated to provide a significant benefit in terms of remission rate and overall survival, despite an enhanced infectious burden [1]. Indeed, febrile neutropenia (FN) episodes are considerably more prevalent in patients receiving such a combination, in spite of the prophylactic measures widely implemented [1]. The outpatient setting of this treatment and the lack of data on the value of prophylaxis in this situation make primary antibiotic prophylaxis a relevant question.

Indeed, antibiotic prophylaxis in neutropenic patients with cancer remains controversial and is not a broadly recommended intervention in the management of patients with

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[a]Xavier Brousse and Nicolas Rasandisona contributed equally to this manuscript.

Correspondence: Xavier Brousse, MD, MSc, Service d'Hématologie Clinique et de Thérapie Cellulaire, 1 av. Magellan, CHU de Bordeaux, F-33604 Pessac, France (xavier.brousse@chu-bordeaux.fr); Pierre-Yves Dumas, MD, PhD, Service d'Hématologie Clinique et de Thérapie Cellulaire, 1 av. Magellan, CHU de Bordeaux, F-33604 Pessac, France (pierre-yves.dumas@u-bordeaux.fr).

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hematological malignancies according to guidelines [2, 3], including in the VEN-AZA regimen [4]. Previous studies have shown that prophylactic treatment with levofloxacin (LEVO) is an effective and well-tolerated strategy to prevent febrile episodes and other relevant infection-related outcomes in patients with cancer and neutropenia, including acute leukemia [5]. However, data on the impact on mortality remain conflicting, according to the population studied [2, 6–8]. Finally, consequences on microbial resistance including extended spectrum β-lactamase (ESBL) bacteria and fluoroquinolone resistance (FQR) strains [2] discouraged the widespread use of this strategy. Last, the risk of increased FQR could decrease the long-term effectiveness of this approach [9].

The aim of this study was to compare the incidence of FN during the first course of VEN-AZA in patients with AML who received LEVO antibiotic prophylaxis versus those who did not.

METHODS

Study Design

This retrospective study included all adult patients in the DATAML registry with newly diagnosed, secondary, or refractory/relapsed AML according to the World Health Organization classification [10], who received at least 1 cycle of VEN-AZA between 1 December 2015 and 31 May 2023. Although some patients underwent multiple courses of VEN-AZA at different times during their disease, they were only included once. Exclusion criteria were acute promyelocytic leukemia and patients allergic to fluoroquinolones. Briefly, DATAML is a French multicentric registry including all patients with AML diagnosed and/or treated in Toulouse and Bordeaux University Hospitals since 2000. A flowchart describing the process of patient selection is available in the Supplementary Appendix (Supplementary Figure 1).

Patients and Treatments

Patients in LEVO and standard of care (SOC) groups were treated in parallel in the same periods. Patients in the LEVO group received antibiotic prophylaxis with LEVO 500 mg daily from day 10 until neutrophil recovery $> 0.5 \times 10^9$/L following the first course of VEN-AZA in an outpatient setting. This prophylactic treatment was carried out according to the protocol established by Toulouse University Hospital. No patient in the SOC group received LEVO prophylaxis during the study. If prophylaxis for patients in the LEVO group was stopped because of adverse events, subsequent infections were still attributed to the LEVO group. Patients in the LEVO group were required to have received at least 1 day of antibiotic prophylaxis. The latter was discontinued once patients had achieved complete remission. The strategy for FN management in the LEVO group was broad-spectrum β-lactam antibiotics (cefepime, ceftazidime, or piperacillin-tazobactam for inpatients) and anti-Gram-positive bacteria antibiotics if deemed clinically appropriate. The strategy for FN in the SOC group was amoxicillin-clavulanate (or cefuroxime) and ciprofloxacin for a minimum of 7 days for outpatients, or broad-spectrum β-lactam antibiotics for inpatients. No exhaustive infectious workup was required for patients treated for FN in an outpatient setting. VEN was administered orally, at 400 mg once daily for 28-day cycles. Ramp-up of VEN was 100, 200, or 400 mg during days 1–3 of the 28-day cycle (or appropriated dose if posaconazole or levofloxacin were also administered). AZA was given at a standard dose of 75 mg/m²/day for 7 days. Bone marrow (BM) assessment was performed at day 21 of cycle 1. Patients with morphological BM blast clearance (<5%) discontinued VEN and received granulocyte colony-stimulating factor at a daily dose of 5 μg/kg until neutrophil recovery. For patients with more than 5% BM blasts at day 21, VEN was continued, and the next AZA course was started at day 28 of cycle 1.

The schedule for the first cycle treatment plan is detailed in Supplementary Appendix (Supplementary Figure 2). Treatment continued until the patient relapsed or until the occurrence of unacceptable toxicity. Most patients received antifungal prophylaxis by posaconazole, leading to decrease VEN at 100 mg/day. Cytogenetic risk was defined according to the Medical Research Council classification [11]. Response to treatment was defined according to European LeukemiaNet (ELN) 2017 criteria [12].

Microbiology

Antimicrobial susceptibility testing was performed by the methods of minimum inhibitory concentration or disk diffusion, according to the European Committee on Antimicrobial Susceptibility Testing and the Antibiogram Committee of the French Society of Microbiology guidelines. Resistance to fluoroquinolones referred to resistance to levofloxacin. For Enterobacterales, if nalidixic acid was determined to be resistant according to antimicrobial susceptibility testing, the strain was not considered resistant to fluoroquinolones (although clinical use is debatable). When required, the presence of ESBL was confirmed using the MAST D68C ESBL and AmpC detection set (MAST Group, Bootle, UK), a combination disk diffusion test.

Outcome

The primary endpoint was the occurrence of an episode of FN during the first follow-up cycle (after day 10) according to the guidelines of the Infectious Diseases Society of America [13]. Secondary endpoints were the occurrence of a clinically documented infection, the occurrence of a microbiologically documented infection, the documentation of ESBL and FQR isolates. Potential adverse events (notably *Clostridioides difficile* infection) were also investigated as well as overall mortality and transfers to intensive care units.

Ethical Statement

Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki, allowing the collection of clinical data in the anonymized French Toulouse-Bordeaux DATAML registry (Commission Nationale de l'Informatique et des Libertés number DR-2015-529).

Statistical Analyses

Before any analysis, a verification phase of missing, aberrant, or inconsistent data took place. At the end of this data validation phase, the updated database was locked. Analyses were carried out on this locked database. Data analyses were performed using Stata software (Statistical Software: Release 18.0 Stata Corporation, College Station, Texas, USA). Continuous data were summarized descriptively including median, interquartile range (IQR p25–p75), minimum and maximum (on the data provided). Categorical data were summarized by numbers and percentages. Percentages were based on the number of patients with no missing data. Comparisons of patient characteristics between the LEVO and the SOC group were assessed using Student *t*-test (or Mann-Whitney test if necessary) for continuous variables, and the χ^2 test (or Fisher exact test if necessary) for categorical variables. Endpoints were compared similarly except for survival free from fever, which was compared using the log-rank test. In multivariable analysis, differences in FN during C1 were compared between the LEVO and SOC groups using a Firth logistic regression model [14] due to the occurrence of rare events among certain categories of variables. Variables initially included into multivariable analyses were LEVO and SOC groups together with all potential confounding factors. Potential confounding factors were gender, age, AML status (considering type of relapse), and posaconazole prophylaxis. Finally, suitability of the logistic regression model to the data was tested using Pseudo-R^2. All reported *P* values were 2-sided, and the significance threshold was set at <.05.

RESULTS

Study Population

A total of 258 patients with AML fulfilled inclusion criteria and were retrospectively included in this study (flowchart on study population available in Supplementary Appendix), respectively 72 (27.9%) in the LEVO group and 186 (72.1%) in the SOC

Table 1. Baseline Characteristics of 258 AML Patients at Diagnosis

	Total N = 258 (100%)	SOC Group N = 186 (72.1%)	LEVO Group N = 72 (27.9%)	*P* Value
Male gender: n (%)	142 (55.0)	102 (54.8)	40 (55.6)	.917
Age (y): median (IQR)	69.8 (59.7–75.4)	69.2 (57.7–74.8)	72.3 (65.1–76.5)	.024
ECOG ≤1 at diagnosis: n (%)	209 (81.6)	152 (82.6)	57 (79.2)	.522
Charlson score ≥ 4[a] n/tested (%)	5/187 (2.7)	3/127 (2.4)	2/60 (3.3)	.657
WBC ($\times 10^9$/L): median (IQR)	5.3 (2.1–20.7)	5.9 (2.3–25.8)	4.0 (2.0–13.2)	.176
Secondary AML [b]: n (%)	111 (43.0)	73 (39.2)	38 (52.8)	.048
Cytogenetic risk: n (%)				
Favorable	8 (3.2)	5 (2.7)	3 (4.2)	.507
Intermediate	163 (63.9)	121 (65.8)	42 (59.2)	
Adverse	84 (32.9)	58 (31.5)	26 (36.6)	
ELN 2017 prognosis: n (%)				
Favorable	58 (24.6)	43 (25.4)	15 (22.4)	.624
Intermediate	57 (24.2)	38 (22.5)	19 (28.4)	
Adverse	121 (51.2)	88 (52.1)	33 (49.3)	
***FLT3*-ITD mutation: n (%)**	22 (8.9)	17 (9.6)	5 (7.4)	.589
***NPM1* mutation: n (%)**	59 (24.5)	45 (26.0)	14 (20.6)	.378
AML status: n (%)				
Newly diagnosed	136 (52.7)	93 (50.0)	43 (59.7)	.206
Refractory	25 (9.6)	25 (13.4)	0 (0%)	.002
Relapses	97 (37.6)	68 (36.6)	29 (40.3)	.567
Morphological relapse	71 (27.5)	46 (24.7)	25 (34.7)	
Other relapses[c]	26 (10.1)	22 (11.8)	4 (5.6)	
Posaconazole prophylaxis: n (%)	175 (68.6)	108 (59.0)	67 (93.1)	<.001
Outpatient setting: n (%)	126 (48.8)	94 (50.5)	32 (44.4)	.379
Antibiotherapy before C1: n (%)	97 (39.1)	70 (39.5)	27 (38.0)	.824

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group performance status; ELN, European Leukemia Net; IQR, interquartile range; ITD, internal tandem duplication; LEVO, levofloxacin; SOC, standard of care; WBC, white blood cells.

[a]Charlson score was available for patients older than age 65 y.

[b]Non de novo AML.

[c]Including molecular and extramedullary.

group. The characteristics of these 258 patients at diagnosis are presented in Table 1. Briefly, 142 (55%) were male, 111 (43.0%) had a secondary AML including 29 (11.2%) progressing from myelodysplastic neoplasm. The median age at diagnosis was 69.8 (IQR 59.7–74.9) years. Characteristics at VEN-AZA initiation are presented in Table 1. More details about patient baseline comorbidities are available in Supplementary Appendix (Supplementary Table 1). Half of the cohort was treated in an outpatient setting without any difference between both groups (32/72 [44.4%] for the LEVO group and 94/186 [50.5%] for the SOC group, $P = .379$). Globally, 136 patients (52.7%) received VEN-AZA as front-line treatment, 97 (37.6%) for relapsed AML and 25 (9.6%) in the setting of refractory AML. None of the patients in the LEVO arm were in in this latter case. Relapses were morphological for 71 patients (73.2%); molecular for 22 (20.6%) and extramedullary for 4 (4.2%).

Very few patients (N = 14, 5.5%) were screened for multiresistant bacteria during the 3 months before VEN-AZA treatment and 12 carried such bacteria without difference between the LEVO and SOC groups ($P = .546$). The median duration of LEVO prophylaxis was 20 days (IQR 15–40, min 2; max 180). After the first course of VEN-AZA, the rate of complete response or complete response with incomplete count recovery was 41.3%.

Febrile Episodes

During the first course of VEN-AZA, FN occurred in 93 patients (36%) without difference between the LEVO (N = 24; 33.3%) and SOC (N = 69; 37.1%; $P = .572$) groups. Multivariable analyses (Table 2) showed that extramedullary and molecular relapses were the only factor independently associated with a decreased risk of FN (adjusted odd ratio, 0.03; 95% confidence interval, .002–.42; $P < .001$) whereas age, gender, posaconazole prophylaxis, and LEVO prophylaxis were not.

Kaplan–Meier estimates of survival free from fever with and without LEVO prophylaxis did not show any difference (Figure 1). However, in patients with FN, the median time to fever was significantly longer in the LEVO group (12.5 days, IQR 8.0–16.5, range 1–28) than in the SOC group (8.0 days, IQR 2.0–12.0, range 1–34; $P = .040$).

Infection Characteristics During the First Course

Among clinically documented infections (Table 3 and Figure 2*A*), statistically, fewer infections (N = 6/72, 8.3%) were reported in the LEVO group than in the SOC group (N = 37/186, 19.9%; $P = .026$). The lung was the most frequent site of infections (7.8%, 20/258 in the entire cohort) but the rate of pneumonia was significantly dramatically reduced by LEVO prophylaxis at 1.4% versus 10.2% in the SOC group ($P = .026$). Other sites of infection were similar in both groups, yet no urinary tract infection was found in the LEVO group.

Microbiologically documented infections occurred in 9.7% of the patients receiving prophylactic LEVO versus 12.9% in the SOC group ($P = .481$) (Table 3). Bacteremia (including central venous catheter-related bloodstream infections [CRBSI]) occurred in 6 patients (8.3%) in the LEVO group versus 20 (10.8%) in SOC the group ($P = .563$) (Figure 2*B*).

The microorganisms responsible for bacteremia are presented in Table 4 and Figure 2*C*. Briefly, patients receiving LEVO

Table 2. Logistic Regression for Factors Independently Associated With Febrile Neutropenia

		Univariate Analysis		Multivariable Analysis	
Variable	n (event)	OR [CI95]	*P* Value	aOR [CI95]	*P* Value
AML status					
Newly diagnosed	136 (58)	1			
Refractory	25 (8)	0.65 [.26–1.55]	.336	0.60 [.23–1.56]	.285
Morphological BM relapse	71 (27)	0.83 [.46–1.48]	.528	0.80 [.41–1.54]	.497
Other relapses	26 (0)	0.03 [.0002–.19]	<.001	0.03 [.002–.42]	**<.001**
Age at VEN-AZA (y)					
≤70	141 (47)	1		1	
>70	117 (47)	1.39 [.83–2.3]	.210	0.88 [.48–1.61]	.683
Gender					
Male	142 (58)	1		1	
Female	116 (36)	0.63 [.37–1.05]	.08	0.72 [.42–1.23]	.232
Levofloxacin prophylaxis					
No	186 (70)	1		1	
Yes	72 (24)	0.85 [.48–1.50]	.585	0.60 [.32–1.12]	.105
Posaconazole prophylaxis					
No	80 (22)	1		1	
Yes	175 (72)	1.94 [1.10–3.51]	.002	1.65 [.88–3.11]	.118

Abbreviations: AML, acute myeloid leukemia; aOR, adjusted odds ratio; BM, bone marrow; CI, confidence interval; VEN-AZA, venetoclax-azacitidine.

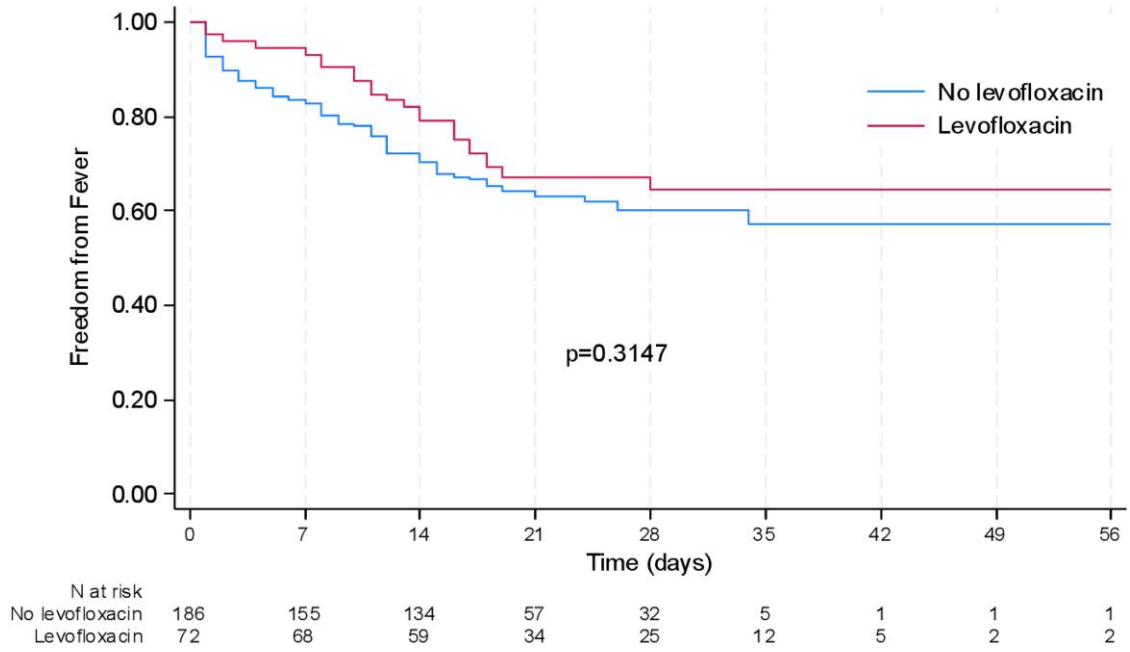

Figure 1. Kaplan–Meier estimates of survival free from fever among all patients.

Table 3. Incidence of Clinically Documented Infections, Fever of Unknown Origin in LEVO and SOC Groups, n (%)

	SOC Group n = 186	LEVO Group n = 72	*P* Value
Fever of unknown origin	32 (17.2)	18 (33.3)	.155
Clinically documented	37 (19.9)	6 (8.3)	.026
Pneumonia	19 (10.2)	1 (1.4)	
Skin and soft-tissue infections	4 (2.1)	1 (1.4)	
Complicated urinary tract infection	4 (2.1)	0 (0.0)	
Intra-abdominal infections	5 (2.7)	1 (1.4)	
Others[a]	5 (2.7)	3 (4.2)	
Microbiologically documented	24 (12.9)	7 (9.7)	.481
Bloodstream infection[b]	20 (10.8)	6 (8.3)	
Urinary tract infection	3 (1.6)	0 (0)	
BAL fluid	1 (0.5)	0 (0)	
Central venous catheter without bloodstream infection	0 (0)	1 (1.4)	
Overall documented infection	61 (32.8)	13 (18.1)	.019

Abbreviations: BAL, bronchoalveolar; LEVO, levofloxacin; SOC, standard of care.

[a]Central venous catheter infection, uncomplicated urinary tract infection.

[b]Including central venous catheter–related bloodstream infections.

prophylaxis had a significantly lower rate of *Enterobacteriaceae* at 1.4% versus 9.1% in the SOC group ($P = .049$).

Focusing on the composite criterion combining documented infections (clinically or microbiologically), a significant difference was observed between the 2 groups with a statistically significantly higher rate of infection in the SOC group (63/186 [32.8%] vs 13/72 [18.1%], $P = .019$) (Table 3). The incidence of fever of unknown origin thus appears to be higher in the LEVO group although this difference is not significant (N = 18; 33.3%) than in the SOC group (N = 32; 17.2%; $P = .155$).

The rates of staphylococci, nonfermenting gram-negative bacilli, and anaerobic infections were low, precluding any comparison. Finally, there was no documented infection by *Enterococcus/Streptococcus* spp in the LEVO group versus 25.8% in the SOC group ($P = .111$). Patients with pathogens resistant to levofloxacin were not significantly more frequent in the LEVO group (N = 5; 7.2%) compared to the SOC group (N = 5; 20.8%; $P = .142$). There was no increased risk of ESBL gram-negative bacilli, with 2 cases reported—1 in each group ($P = 1.0$).

Duration of Antibiotherapy, Intensive Care Unit Admission and Side Effects

All patients with FN in the LEVO group (N = 24, 33.3%) were hospitalized and received a subsequent line of broad-spectrum antibiotherapy for a median duration of 10 days (range 2–45; IQR 7–15), wheres this was the case for 50 (26.9%) patients in the SOC group ($P = .382$) for a median of 11.5 days (IQR 7–15; range 1–46; $P = .850$). For patients in the SOC group who received amoxicillin-clavulanate (or cefuroxime) and ciprofloxacin in an outpatient setting, the median duration of treatment was 7 days (IQR 7–7; range 4–10).

Of the 258 patients included in the study, 11 (4.3%) were transferred to an intensive care unit, 1 (1.4%) in the LEVO group and 10 (5.4%) in the SOC group ($P = .298$). Five of these transfers were due to sepsis (45.5%), the others being for respiratory or neurological failure. Microbiological documentation was available for 4 of the sepsis patients, respectively

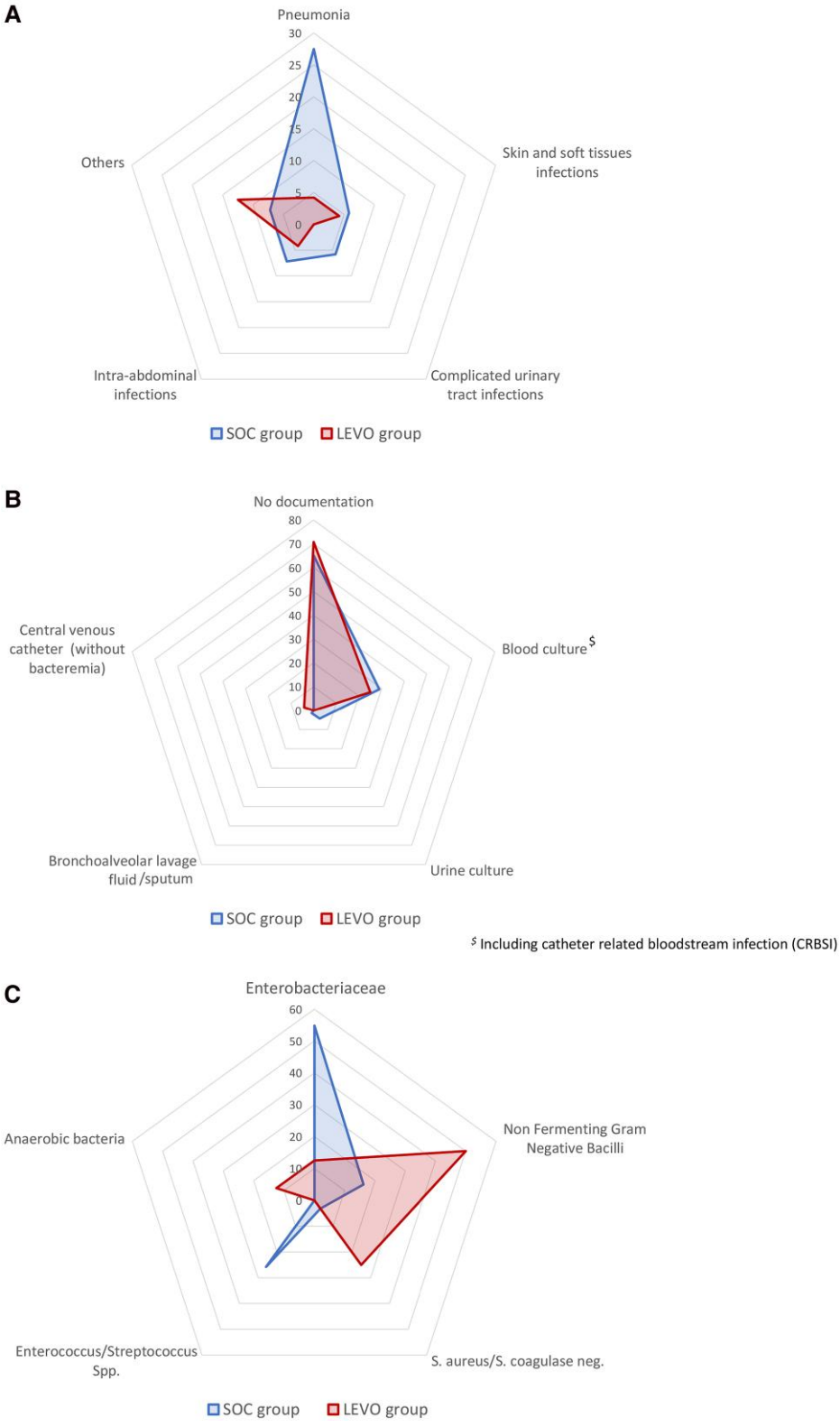

Figure 2. *A*, Radar plot for the distribution of infection focus among clinically documented infections (%). (*B*) Radar plot for the distribution of microorganisms among microbiologically documented infections (%). (*C*) Radar plot for the distribution of responsible pathogens among all microorganisms documented (%).

Table 4. Distribution of Microorganisms and Resistance in LEVO and SOC Groups, n (%)

Isolates	SOC Group n = 186	LEVO Group n = 72	*P* Value
Enterobacteriaceae	17 (9.1)	1 (1.4)	.029
Pseudomonas aeruginosa/ Stenotrophomonas maltophilia	5 (2.7)	4 (5.6)	.271
Staphylococcus aureus/ Staphylococcus coagulase negative	1 (0.5)	2 (2.8)	.189
Enterococcus/Streptococcus spp.	8 (4.3)	0 (0.0)	.111
Anaerobic bacteria	0 (0.0)	1 (1.4)	.279
Phenotypical resistance[a]	SOC group	LEVO group	
Levofloxacin resistance	5 (7.2)	5 (20.8)	.142
ESBL	1 (1.4)	1 (4.2)	1.00

One patient can have several documentations.

Abbreviations: ESBL, extended spectrum β-lactamase; LEVO, levofloxacin; SOC, standard of care.

[a]Among patients with febrile neutropenia.

Klebsiella variicola bacteremia (n = 1), FQR, and methicillin-resistant *Staphylococcus haemolyticus* CRBSI (n = 1), *Pseudomonas aeruginosa* bacteriemia (n = 1), and severe *Pneumocystis* pneumonia (n = 1). The patient with the coagulase-negative staphylococcus CRBSI was in the LEVO group, whereas the others were in the SOC group. The overall 30-day mortality was 0/72 (0%) in the LEVO group compared to 9/186 (4.8%) in the SOC group (0.128). Finally, during the first VEN-AZA course, none of the patients in the LEVO group died from an infection versus 5 from the SOC group. These SOC patients died from *Pneumocystis* pneumonia (n = 1), SARS-CoV-2 infection (n = 1), undocumented pneumopathy (n = 1), or *P aeruginosa* infection (n = 2). For the latter 2, 1 was associated with mucormycosis and SARS-CoV-2, whereas the other was documented with a FQR strain infection.

Seven (9.7%) patients receiving LEVO had adverse events (AEs) attributed to prophylaxis, respectively grade 1–2 musculoskeletal AE (n = 1), cutaneous AEs (n = 3, 2 drug eruptions and 1 Drug Reaction with Eosinophilia and Systemic Symptoms syndrome), gastrointestinal AEs (nausea, vomiting n = 2), and 1 neurological AE (confusion). *Clostridioides difficile* colitis was detected in 2 patients, both in the SOC group.

DISCUSSION

In this retrospective study, the incidence of FN was comparable with or without LEVO prophylaxis during the first course of VEN-AZA, with an incidence of 33.3% compared to 37.1% in the SOC group. The absence of difference may be due to insufficient statistical power. This rate is close to the 42% incidence reported in patients treated with VEN-AZA in the VIALE-A study [1]. Multivariable analyses confirmed the absence of any significant independent impact of LEVO prophylaxis on the incidence of FN, whereas molecular/extramedullary relapse was significantly and independently associated with a decreased risk, most likely from the absence of BM blasts, thus decreasing the risk of grade 4 neutropenia [15].

LEVO prophylaxis decreased the incidence and the profile of clinically and microbiologically documented infections. In the SOC group, most infectious cases were pneumonia, as in the VIALE-A study, where this was the most frequent clinical presentation, occurring in ~20% of the cases. Interestingly, the incidence of pneumonia was dramatically decreased in patients receiving LEVO, as were urinary tract infections. Among FN cases, only one third had a microbiologically documented infection raising the possibility of fevers of noninfectious origin [16].

Gram-negative bacteria appeared to be the main species responsible for microbiologically documented infections, Enterobacterales with *Escherichia coli* being the most frequently identified, followed by *P aeruginosa*. Whereas previous studies tended to report a higher proportion of gram-positive cocci infections in hematology patients, these results, in line with previous publications [17, 18], are probably explained by the less frequent use of a central venous catheter. Moreover, as severe colitis is an infrequent AE with VEN-AZA, this might explain the low incidence of bloodstream infections with streptococci as compared to intensive chemotherapy. Deaths from infectious causes were partly due to nonbacterial infections, yet all occurred in the SOC group. One SOC patient died of septic shock with *P aeruginosa* bloodstream infection documented with a strain resistant to LEVO. Other causes of infection-related death were not exclusively from bacterial origin. Finally, major AEs were rare among patients receiving LEVO prophylaxis but 5/7 patients who experienced AEs stopped prophylaxis.

The question of a rising risk of selection of FQR germs is a major one in the context of antibiotic prophylaxis. However, no significant difference was observed in the documentation of resistant germs (ESBL or fluoroquinolone resistance) between the 2 groups. In the context of FN, where microbiological documentation is infrequent, the identification of resistant germs remains a rare occurrence. The absence of difference could be attributed to the fact that some febrile patients in the SOC group were treated with a combination of ciprofloxacin and amoxicillin/clavulanic acid and thus also exposed to fluoroquinolones [2, 19]. Furthermore, it is possible that some patients with FN in the SOC group, treated in an outpatient setting, did not benefit from a complete infectious workup. It is therefore possible that the difference in the rate of microbiological documentation is in fact even greater between the 2 groups.

Finally, although it could be argued that differences observed in the present study could be due to a center effect, it must be stressed that protocols in both centers were relatively similar, except for prophylaxis prescription, making it unlikely that this factor alone could fully explain such a difference.

To our knowledge, this is the first study to focus specifically on the impact of LEVO as primary prophylaxis in patients with AML treated with the VEN-AZA combination, on the incidence of FN and the risk of bacterial infections. Nevertheless, this study has obvious limitations due to its retrospective nature, mainly based on medical records, which may lead to a lack of reliability regarding the occurrence or nonoccurrence of fever at home. Despite the use of adjusted models, no less robust than propensity score analysis [20], the 2 groups differed on some characteristics, and it is possible that unmeasured confounding factors may have contributed to the differences observed between these 2 populations. Finally, because of the scarcity of microbiological data among neutropenic patients, establishing a difference in resistant strains was obviously challenging. The absence of monitoring for stool cultures or rectal swabs is a limitation, hindering the documentation of colonization by ESBL-producing bacteria of FQR strains.

In conclusion, a short course of LEVO as primary prophylaxis in patients with AML treated with VEN-AZA appeared to decrease the rate of clinically or microbiologically documented infections. However, the incidence of FN was not significantly decreased. This prophylaxis impacts the pattern of clinically and microbiologically documented infections. Whether LEVO influences FQ resistance is debatable because patients with hematological malignancies are regularly exposed to broad-spectrum antibiotics, including fluoroquinolones. Obviously, the current study deserves further investigations in a prospective randomized trial with appropriate power to provide a definitive and clear answer to this major question.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Access to data. Some deidentified data will be shared with other researchers upon reasonable request to the alternate corresponding author (pierre-yves.dumas@u-bordeaux.fr). Sharing will require a detailed proposal to the study investigators, and a data transfer agreement must be signed.

Potential conflicts of interest. Xavier Brousse, Nicolas Rasandisona, Emilie Bérard, Harmony Leroy, Karen Delavigne, Nathan Mottal, Suzanne Tavitian, Thibaut Leguay, Léopoldine Lapierre, Eric Delabesse, Audrey Bidet, Martin Gauthier, Diane Lara, Anne Banos, Jennifer Guiraud, Pauline Floch, Audrey Sarry, Anne-Charlotte de Grande, Clémentine Béranger, Christian Récher, Arnaud Pigneux, Sarah Bertoli, and Pierre-Yves Dumas have no disclosure. All other authors report no potential conflicts.

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