Sociedade Brasileira de Infectologia

The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Original Article

Safety of levofloxacin as an antibiotic prophylaxis in the induction phase of children newly diagnosed with acute lymphoblastic leukemia: an interim analysis of a randomized, open-label trial in Brazil

Mauro Cesar Dufrayer [a,*], *Ciliana Rechenmacher* [c,e], *Clarice Franco Meneses* [b], *Yasmine Massaro Carneiro Monteiro* [c], *Fabianne Altruda de Moraes Costa Carlesse* [d], *Fabrizio Motta* [a], *Liane Esteves Daudt* [b,c,e], *Mariana Bohns Michalowski* [b,c,e]

[a] *Hospital da Criança Santo Antônio, Porto Alegre, RS, Brazil*
[b] *Hospital de Clínicas de Porto Alegre (HCPA), Serviço de Oncologia Pediátrica, Porto Alegre, RS, Brazil*
[c] *Universidade Federal do Rio Grande do Sul (UFRGS), Departamento de Pediatria, Porto Alegre, RS, Brazil*
[d] *Universidade Federal de São Paulo (UNIFESP), Instituto de Oncologia Pediátrica – GRAACC, São Paulo, SP, Brazil*
[e] *Hospital de Clínicas de Porto Alegre (HCPA), Laboratório de Pediatria Translacional, Serviço de Pesquisa Experimental, Porto Alegre, RS, Brazil*

ARTICLE INFO

Article history:
Received 9 August 2022
Accepted 5 January 2023
Available online 5 February 2023

Keywords:
Acute lymphoblastic leukemia
Pediatric
Fluoroquinolone
Induction
Prophylaxis
Levofloxacin
Febrile neutropenia

ABSTRACT

Background: Despite high cure rates, treatment-related mortality in children with acute lymphoblastic leukemia (ALL) remains significant. About 4% of patients die during remission induction therapy and approximately two-thirds of treatment-related deaths are due to infectious complications.

Methods: From May 2021 to June 2022, children aged one through 18 years, with a recent diagnosis of ALL, admitted to three pediatric oncology centers in Brazil, were enrolled in this multicenter, open-label, randomized, phase 3 clinical trial. Eligible patients were randomly divided into two groups, based on a 1:1 allocation ratio, to receive, or not, levofloxacin as a prophylactic agent during the induction phase. All patients were treated according to the IC-BFM 2009 chemotherapy protocol. Primary endpoints were carbapenemase-producing Enterobacteriaceae (CPE) colonization, *Clostridioides difficile* diarrhea, and other adverse events related to the use of levofloxacin. The secondary endpoint was febrile neutropenia during induction. The median follow-up was 289 days.

Results: Twenty patients were included in this trial, 10 in each group (control and levofloxacin). Mild adverse reactions related to levofloxacin were observed in three patients (30%). Three patients had *Clostridioides difficile* diarrhea, two in the levofloxacin group and one in the control group ($p > 0.99$). Only one patient presented colonization by CPE. This patient belonged to the levofloxacin group ($p > 0.99$). Nine patients presented febrile neutropenia,

* Corresponding author.
E-mail address: mauro.dufrayer@santacasa.org.br (M.C. Dufrayer).

https://doi.org/10.1016/j.bjid.2023.102745

five in the control group and four in the levofloxacin intervention group ($p > 0.99$), one patient died due to febrile neutropenia.

Conclusion: The use of levofloxacin was shown to be safe in the induction phase in children with *de novo* ALL. The use of this medication did not increase the rate of colonization by CPE nor the rate of diarrhea by *C. difficile*. All adverse reactions were mild and remitted either spontaneously or after switching medicine administration from oral to intravenous route.

Introduction

Malignant neoplasms are the leading cause of disease-related childhood deaths and, among them, acute lymphoblastic leukemias (ALLs) are the most prevalent.[1] ALLs can be defined as a heterogeneous group of diseases manifested by the proliferation of immature lymphoblasts in the marrow, in peripheral blood or on other tissues. It is basically treated with high-dose polychemotherapy, followed by a maintenance phase consisting of low-dose chemotherapy.[2]

Despite the positive evolution of treatment over the last decades –with a global survival rate close to 90%[3] – treatment-related mortality (TRM) remains significant: about 4% of patients die during remission induction therapy. Approximately two-thirds of these deaths are due to infectious causes.[4]

Bacteria can thus be perceived as one of the main causative agents of morbidity and mortality in patients with chemotherapy-related neutropenia. In adults, significant benefits were demonstrated with the use of antibiotic prophylaxis during these periods, as they reduced infections and lowered rates of infection-related mortality.[5] While the use of antibiotic prophylaxis in adult patients during periods of afebrile neutropenia is already a well-established practice, we lack solid evidence concerning its use in children.

Levofloxacin, a broad-spectrum fluoroquinolone antibiotic, is included in guidelines and indicated to afebrile neutropenic adult patients. According to a recommendation published by The Infectious Diseases Society of America (IDSA) in July 2020, the regular use of antibiotic prophylaxis for children with *de novo* ALL is not indicated during the induction phase precisely because of the low body of evidence that exists. When necessary, the IDSA suggests levofloxacin as the antibiotic of choice and only for patients with severe neutropenia (absolute neutrophil count < 500/mm^3) for at least seven days.[6]

In spite of the scarcity of currently available information, a few observational studies on the use of levofloxacin and one randomized trial in children with relapsed ALL have been published. Wolf et al. demonstrated that levofloxacin reduced the odds of febrile neutropenia, bacterial infection, and bloodstream infection during the induction therapy of children with LLA. Surprisingly, it also reduced the chances of infections from *C. difficile* without breakthrough infections with antibiotic-resistant organisms.[7] Similarly, Sulis et al. verified that the use of Fluoroquinolones (levofloxacin or moxifloxacin) for prophylaxis in children with an initial diagnosis of ALL receiving induction chemotherapy was effective in reducing Gram-negative and some Gram-positive bacteremia. Moreover, no increased incidence of multidrug-resistant microorganism, *C. difficile* infection, or fungi was observed.[8]

Considering the promising activity of levofloxacin in preventing febrile neutropenia and the lack of knowledge regarding its possible adverse effects in the induction phase, we conducted the present study to assess the safety and efficacy of this antibiotic medication in children newly-diagnosed with ALL during the induction phase. This preliminary interim analysis aims to ensure greater safety for the patients contemplated in this study and allows the continuation of the clinical trial.

Material and methods

Trial design, oversight, and participants

From May 2021 to June 2022, children aged one through 18 years, with newly-diagnosed ALL admitted at three pediatric oncology centers in Brazil, who completed induction therapy before 30 June 2022, were enrolled in this multicenter, open label, randomized, phase 3 clinical trial. Children with any type of allergy to the use of quinolones and a history of chronic arthritis undergoing treatment were not included in the study. Children with clinically or microbiologically documented infection prior to initiation of induction, as well as those with fever prior to induction therapy that required prolonged antibiotic therapy (> 5 days) to treat infection, were not included in the study in order to avoid confounding antibiotic treatment with antibiotic prophylaxis. Likewise, children with any form of allergy to quinolones or with a history of chronic arthritis treatment were not included in this trial. Patients who developed febrile neutropenia within the first seven days of induction or after up to two days of neutropenia were excluded due to the lack of sufficient time for antibiotic prophylaxis activity.

The trial protocol was approved by the ethics committee or institutional review board at each of the participating centers (CAAE 43,076,621.8.2001.5683). The children's parents or legally acceptable representatives provided written informed consent.

Randomization

Eligible patients were randomly assigned in a 1:1 ratio by a computer-generated number. During the induction phase, patients would either be given levofloxacin (intervention group) as a prophylactic agent or no prophylaxis (control group).

Treatment

All patients were treated according to the IC-BFM 2009 chemotherapy protocol. Patients in the intervention group started using levofloxacin on the third day after the beginning of induction and its use was continued until any of the following criteria were met: (a) absolute neutrophil count greater than or equal to 500/μL after nadir; (b) start of the next cycle of chemotherapy; (c) use of parenteral antibiotic therapy for any reason.

Children aged 1 to < 5 years were given a dose of 10 mg/kg/dose of levofloxacin, twice a day; children older than five years were prescribed 10 mg/kg/dose once a day, with a maximum dose of 750 mg a day. Levofloxacin was administered orally but, if the oral route was not tolerated, it could be administered intravenously at the same dose and schedule.

Although the control group did not receive levofloxacin as primary prophylaxis, both groups received trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis jirovecii*.

All patients from both groups received induction therapy that included four weeks of oral prednisone, fours weekly doses of vincristine, two or four weekly doses of daunorubicin, and two doses of PEG-asparaginase.

Outcomes and assessments

The primary endpoints were CPE colonization, *C. difficile* diarrhea, and adverse events related to the use of levofloxacin. The second endpoint was febrile neutropenia during induction.

C. difficile diarrhea was defined by the presence of diarrhea and identification of *C. difficile* in stools by PCR or presence of its toxins.

CPE colonization monitoring was performed by rectal swab at the time of admission to the hospital and at the end of the induction phase. Any additional swab collection was at the discretion of the physician or Hospital Infection Control team of each center.

Febrile neutropenia was defined by the presence of axillary body temperature greater than or equal to 37.8 °C in patients whose total neutrophil count was below 500/μL.

Adverse effects were defined in terms of causality and classified as: possible, likely, or certain. They were also described regarding the severity of each physiological system and classified as: mild, moderate, severe or fatal, according to modified criteria of the World Health Organization (Tables 1 and 2).[9]

Table 1 – WHO classification of toxicity as causality.

Possible	Occurs where two or more medications may be involved, or it can be inferred relationship with the disease
Likely	Occurs where only one drug may be involved
Certain	Occurs during infusion and/or re-exposure

Statistical methods

This study is ongoing and data for this interim analysis were collected on June 23, 2022 after 18 months of initiation. Efficacy and safety analyses included all patients who completed induction phase chemotherapy. Initial target enrollment for the main cohort of the study was 196 patients for the outcome febrile neutropenia, 98 in each group.

Qualitative variables were summarized as absolute and relative frequencies and differences were considered significant at $p < 0.05$ (2-tailed). Data were compiled using the REDCap® web application and analyzed using the PASW Statistics Version 18.0. Fisher's exact test and Pearson's chi-square test were used for categorical variables, and the Mann–Whitney U test for quantitative variables. The binomial proportion confidence interval for the occurrence of adverse events was calculated using the Clopper-Pearson interval.

Results

Twenty patients were included in the interim analysis: Ten in the control group and 10 in the intervention group, who received prophylaxis with levofloxacin. Table 3 shows the characteristics of each group. The median follow-up was 289 days (27 - 394 days). The median duration of levofloxacin use was 29 days (23 - 37 days).

Only one death, due to sepsis by *Pseudomonas aeruginosa*, was observed in the control group. The patient was a male with Down syndrome who died on the thirtieth day of induction. Among the 10 patients who received levofloxacin, three had adverse reactions classified as mild and probably related to levofloxacin. Two patients suffered from nausea, so it was necessary to switch administration of medication from oral to intravenous with cessation of symptoms. One (1) patient had a transient increase in hepatic transaminases, reaching levels up to five times the upper level of normality. Interruption of levofloxacin was not necessary (Table 4).

Three patients had *C. difficile* diarrhea, two in the levofloxacin group and one in the control group ($p > 0.99$). Only one

Table 2 – WHO Classification of toxicity as severity.

Mild	Small clinical and short-term importance, which may require treatment, not substantially affecting the patient's life
Moderate	Alters the patient's usual activities, resulting in transient disability without sequelae. Needs intervention
Severe	Directly threatens the patient's life, causes hospitalization, and can cause permanent sequelae
Fatal	Results in death

Table 3 – Characteristics of the patients included in the analysis.

	Patients, No (%)[a]		
Characteristics	No Prophylaxis (n = 10)	Levofloxacin (n = 10)	p-Value[b]
Age, median (IQR), y	8.0 (2–13.5)	9.5 (2–14.0)	.971
Sex			>0.99
Male	6 (60)	7 (70)	
Female	4 (40)	3 (30)	
Down Syndrome	1 (10)	1 (10)	>0.99
ALL type			>0.99
B	8 (80)	9 (90)	
T	2 (20)	1 (10)	

Abbreviations. ALL, acute lymphoblastic leukemia; IQR, interquartile range; y, year(s).

[a] Data represent No. (%) of patients except otherwise specified.
[b] Fisher's exact test was used for categorical variables and the Mann–Whitney U test for quantitative variables.

Table 4 – Incidence of related adverse events.

	Patients, No (%)			
	No Prophylaxis		Levofloxacin	
Outcome	(n = 10)	(n = 10)	p-Value[a]	95% CI[b]
C. difficile diarrhea	1 (10)	2 (20)	>0.99	–
Febrile Neutropenia	5 (50)	4 (40)	>0.99	–
CPE colonization	0 (0)	1 (10)	>0.99	–
AEs related to levofloxacin	–	3 (30)	–	6.7 – 65.2

CPE, carbapenemase-producing Enterobacteriaceae; AEs, adverse events.

[a] Fisher's exact test was used.
[b] Clopper-Pearson Confidence Interval.

patient assigned to the levofloxacin group presented colonization by CPE in this study identified as *Klebsiella* spp. Similarly, no significant difference was observed between the groups ($p > 0.99$).

Nine patients presented febrile neutropenia in the study, five in the intervention group, and four in the control group. No significant difference between groups was observed ($p > 0.99$).

Discussion

In this preliminary multicenter analysis, the use of levofloxacin showed to be safe in children newly diagnosed with ALL during the induction phase. Its use did not increase the rate of colonization by CPE nor the rate of diarrhea by *C. difficile*. Despite the significant number of adverse reactions related to its use, all were mild and remitted either spontaneously or by switching administration of medication to the intravenous route.

Among the few available data on the use of levofloxacin with children, a cohort study carried out in 2017 at St. Jude Children's Research Hospital (Memphis/Tennessee) with 344 patients found that prophylaxis was able to significantly prevent FN and systemic infection during induction chemotherapy by ≥70%. The use of levofloxacin in these children also minimized the use of antibiotic treatment with cefepime/ceftazidime, vancomycin, and aminoglycosides. Unexpectedly, prophylaxis with levofloxacin also dramatically reduced colitis infection rates caused by *Clostridioides difficile* and other enterocolitis. This is extremely relevant information since infection with *Clostridioides difficile* is related to higher mortality in hospitalized children, higher hospital costs, and longer hospital stays.[7]

In the same year, Sulis et al. corroborated these findings by demonstrating that FQ use for the initial treatment of fever, as well as for prophylaxis in 230 children with an initial diagnosis of ALL receiving induction chemotherapy, was effective in reducing Gram-negative and some Gram-positive bacteremia. In addition, it was shown that levofloxacin did not lead to increased incidence of multiresistant microorganisms nor infections by *C. difficile* or fungi.[8]

The present study, a randomized clinical trial, is the first conducted in Brazil to assess safety and infectious outcomes with the use of levofloxacin in children with an initial diagnosis of ALL in the induction phase.

Due to the history of arthropathies in animal models, the potential to induce bacterial resistance, and fluoroquinolone-resistant *C. difficile* diarrhea, an interim analysis was essential to allow the clinical trial to continue, ensuring greater safety for the observed patients.

While long-term use of levofloxacin may increase the incidence of antibiotic resistance and the development of *C. difficile* diarrhea, the GIMEMA study and a recent meta-analysis of randomized controlled trials demonstrated that these potential facts did not impact infectious outcomes.[10-12]

The study has some limitations. It was not powered to detect differences between the evaluated outcomes. The high number of patients admitted with fever, requiring prolonged antibiotic therapy, significantly reduced sample size. Most importantly, the study was not blinded. Awareness of allocation could affect patient care decisions.

The results shown here allow for the continuity of the study, as acute toxicity or emergence of multidrug-resistant strains were not observed in the group undergoing intervention (use of FQ). Evidently, it is not possible to assess, at this time, any impact on rates of febrile neutropenia or ICU admissions, as the number of patients evaluated is insufficient to analyze these outcomes. Such aspects will be better approached at the end of the study.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

This work received financial supports from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). This research was supported by the Research and Event Incentive Fund (FIPE) of the Porto Alegre Clínicas Hospital (HCPA).

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
2. Pizzo P.A., Poplack D.G., Adamson P.C., Blaney S.M., Helman L. Principles and practice of pediatric oncology. 2016 [cited 2021 Mar 27]. Available from: http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=1473212
3. Pui CH, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. J Clin Oncol. 2015;33:2938–48.
4. Prucker C, Attarbaschi A, Peters C, Dworzak MN, Pötschger U, Urban C, et al. Induction death and treatment-related mortality in first remission of children with acute lymphoblastic leukemia: a population-based analysis of the Austrian Berlin-Frankfurt-Münster study group. Leukemia. 2009;23:1264–9.
5. Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, van de Wetering MD, Kremer LC, Leibovici L. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev. 2012;1:CD004386.
6. Lehrnbecher T, Fisher BT, Phillips B, Alexander S, Ammann RA, Beauchemin M, et al. Guideline for antibacterial prophylaxis administration in pediatric cancer and hematopoietic stem cell transplantation. Clin Infect Dis. 2020;71:226–36.
7. Wolf J, Tang L, Flynn PM, Pui CH, Gaur AH, Sun Y, et al. Levofloxacin prophylaxis during induction therapy for pediatric acute lymphoblastic leukemia. Clin Infect Dis. 2017;65:1790–8.
8. Sulis ML, Blonquist TM, Stevenson KE, Hunt SK, Kay-Green S, Athale UH, et al. Effectiveness of antibacterial prophylaxis during induction chemotherapy in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2018;65:e26952.
9. Red-PARF-5-Port.pdf [Internet]. [cited 2022 Jul 7]. Available from: https://www.paho.org/hq/dmdocuments/2011/Red-PARF-5-Port.pdf
10. Gafter-Gvili A, Paul M, Fraser A, Leibovici L. Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. J Antimicrob Chemother. 2007;59:5–22.
11. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med. 2005;142:979–95.
12. Leibovici L, Paul M, Cullen M, Bucaneve G, Gafter-Gvili A, Fraser A, et al. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer. 2006;107:1743–51.