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Antibiotic prophylaxis: a chance to reduce infections during childhood leukemia treatment

Natalia Zaj[1], Wojciech Makuch[1], Monika Lejman[2], Joanna Zawitkowska[3*]

[1]Student Scientific Society, Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Lublin, Poland

[2]Laboratory of Genetic Diagnostics, Medical University of Lublin, Lublin, Poland

[3]Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Lublin, Poland

Abstract

The curability of childhood leukemia has significantly increased in recent years. The 5-year survival rate for children with acute lymphoblastic leukemia (ALL) now exceeds 90%, and is 65–70% for acute myeloblastic leukemia (AML) patients. Improvements in supportive care, better understanding of biological features of leukemia cells, better recognition of high-risk children, and optimization of treatment regimens through national and international collaboration have led to tremendous progress.

However, the most common and serious complications during antileukemic treatment are infections, mainly bacterial. Literature data shows that antibiotic prophylaxis reduces bacteremia and improves outcomes of adult patients during aggressive chemotherapy. However, the use of antibiotic prophylaxis in pediatric cancer is still controversial. There is a lack of evidence regarding its effectiveness and the best choice of antibiotic. In this review, we summarize the current knowledge on antibiotic prophylaxis in children with leukemia undergoing intensive chemotherapy, considering also antibiotic efficacy and resistance.

Key words: leukemia, antibiotic prophylaxis, children, levofloxacin, ciprofloxacin, moxifloxacin

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Introduction

The curability of childhood leukemia has significantly increased in recent years. The 5-year survival rate for children with acute lymphoblastic leukemia (ALL) now exceeds 90%, and is 65–70% for acute myeloblastic leukemia (AML) patients. Improvements in supportive care, better understanding of biological features of leukemia cells, better recognition of high-risk children, and optimization of treatment regimens through national and international collaboration, have led to tremendous progress [1–5].

However, despite the improvement in cure rates, the most common and serious complications during antileukemic treatment are infections, mainly bacterial [6–9]. Many studies show that Gram-positive bacteria are a significant etiological factor causing infections during ALL and AML treatment in children [10–14]. The most common complications related to infections are infections of the bloodstream, upper respiratory tract, gastrointestinal tract, and ear. Infections interrupt leukemia treatment and prolong hospitalization [15].

Treatment-related mortality is estimated to be 2–4% in current ALL trials, with infections accounting for the majority of deaths [9, 16]. Mortality ranges from 3% to 15% in patients treated for AML [17]. An increased risk of infection during chemotherapy is associated with the use of

*Address for correspondence: Joanna Zawitkowska, Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Gębali 6, 20–093 Lublin, Poland, e-mail: jzawitkowska1971@gmail.com

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central catheters, prolonged neutropenia, the coexistence of Down's syndrome, female gender, young age, and also Caucasian race [9, 11, 15, 16, 18, 19].

Literature data shows that antibiotic prophylaxis reduces bacteremia and improves outcomes of adult patients during aggressive chemotherapy [20]. In 2016, the guidelines drawn up by the National Comprehensive Cancer Network (NCCN), which were approved in hematological malignancies, recommended fluoroquinolones prophylaxis for adult patients [21]. The use of antibiotic prophylaxis in pediatric cancer is still controversial, and there is a lack of clear evidence of its effectiveness and the best choice of antibiotic [22]. The 8th European Conference on Infections in Leukemia (ECIL-8) did not support routine antibiotic prophylaxis in patients with acute leukemias [23]. Empirical antibiotic therapy is a standard procedure in the treatment of children and adults, in the case of neutropenia at the beginning of fever or other infection-related symptoms [24–26].

However, many studies have shown that the prophylactic use of levofloxacin in patients with ALL and AML has resulted in a significant reduction in bacteremia [22, 27]. On the other hand, increasing bacterial resistance is a major concern with prophylaxis [28–31]. The introduction of antibiotic prophylaxis is associated with an increased risk of fluoroquinolone-resistant Gram-negative strains development, which has been demonstrated among patients receiving fluoroquinolone prophylaxis [28, 32]. The choice of antibiotic prophylaxis ought to be considered with local epidemiology-resistance patterns [33]. Additionally, potential adverse effects of antibiotic prophylaxis use, including drug toxicities, invasive fungal disease (IFD) and *Clostridioides difficile* (*C. difficile)* infection, have been described [34]. In this context, it is important to mention musculoskeletal negative side effects, which were observed one year after levofloxacin administration in children and have been described in a few studies [35, 36]. These negative side effects are discussed in the following sections.

In this review, we summarize the current knowledge of antibiotic prophylaxis in children with acute leukemias undergoing intensive chemotherapy, antibiotic efficacy and resistance.

Efficacy of antibiotic prophylaxis during leukemia treatment

Levofloxacin prophylaxis

Fluoroquinolones, as broad-spectrum antibiotics, are a significant class of antibacterial agents. Quinolones inhibit DNA synthesis by blocking the activity of DNA gyrase and topoisomerase IV. DNA gyrase is an enzyme which cannot be found in eukaryotic cells and it is a significant factor for bacterial growth. Levofloxacin, which is classified as the third-generation fluoroquinolone, shows stronger activity against Gram-positive strains than the second-generation group that includes ciprofloxacin [37]. Wolf et al. [22] described the efficacy of levofloxacin prophylaxis use during the induction phase in newly diagnosed patients with acute lymphoblastic leukemia between October 2007 and January 2016. A total of 344 pediatric patients participated in this study. Sixty-nine of those patients received the above-mentioned broad-spectrum antibiotic, and 102 of them received other antibiotics such as ciprofloxacin, cefepime and vancomycin. The remaining 173 patients received no antibiotic prophylaxis. The dose of antibiotic and the exposure duration were selected individually. This single-center cohort trial showed decreased episodes of fever, enterocolitis, bacteremia and general infections, including *Clostridium difficile* (*C. difficile)* infections, thanks to the use of levofloxacin during induction therapy. Children who received levofloxacin prophylaxis had a risk of bacterial infections that was more than halved compared to the group of patients who did not receive prophylaxis (15.9% vs. 37%) [22]. In the study by Sulis et al. [38], 230 patients, aged 1–21, with newly diagnosed ALL, received fluoroquinolones prophylaxis during induction chemotherapy. Children enrolled in that trial were receiving oral or intravenous levofloxacin or moxifloxacin. Therapy was applied to patients without fever. For patients who developed fever, the antibiotic was changed to a broad spectrum one and was administered intravenously. The results were compared to the other ALL Consortium Protocol 05-001 Dana-Farber Cancer Institute. The study showed a remarkable reduction of bacteremia incidents (10.9 vs. 24.4), especially those caused by Gram-negative strains, in pediatric patients undergoing the induction phase. The scientists noticed a significant reduction of infection frequency caused by *Streptocccus viridans* (*S. viridans*) and *Staphylococcus aureus* (*S. aureus*) [38].

In another trial by Alexander et al. [27], patients aged six months to 21 years with AML or relapsed ALL were randomly assigned to one of two groups. One group received levofloxacin prophylaxis (n = 100), while the other received no antibiotics (n = 100). Patients aged six months to five years received a dose of 10 mg/kg of levofloxacin twice a day, whereas patients older than five years received the same dose, but only once a day. The antibiotic was administered orally, or when this was not possible intravenously, on the first or third day of chemotherapy during two cycles. The percentage of bacteremia was much lower in the levofloxacin prophylaxis group of patients (21.9% vs. 43.4%), and there was a lower risk of neutropenia and fever (71.2% vs. 82.1%). Despite the positive effects of this antibiotic, a large number of infections were still observed — *S. viridans* and Gram-negative bacteremia. No influence on the risk of infection frequency caused by the mentioned pathogens suggests a dependence on the spectrum of activity or a lower absorption of the antibiotic by the oral administration. A significant conclusion of the study is that the use

of antibiotic was not associated with an increased risk of musculoskeletal toxic effects, IFD or *C. difficile* infection in the levofloxacin prophylaxis group of patients [27]. Moreover, in the study of Bradley et al. [36], the risk of cartilage injury caused by levofloxacin appears to be uncommon, and musculoskeletal events are clinically undetectable after five years of therapy or are reversible. An American retrospective cohort study conducted for four years enrolled patients aged 6 months to 21 years with AML and relapsed ALL. The pre-implementation group contained 63 patients, and the post-implementation group, in which patients were receiving levofloxacin prophylaxis, contained 72 patients. The main goal of this trial was to examine the influence on the bloodstream infection (BSI) risk and central line associated bloodstream infections (CLABSI), as a result of implementing levofloxacin prophylaxis. The authors reported that bacteremia cases caused by Gram-negative microorganisms significantly decreased in patients in the post-implementation group. Researchers observed more frequent BSI incidents due to levofloxacin-resistant Gram-negative strains presence. Therefore, it is important to pay attention to this possible problem, which is resistance, in the future [39]. The use of antibiotic prophylaxis brings on current-period expense, which is drug cost and antimicrobial resistance caused by the routine introduction of antibiotics [3, 40]. A cost-utility analysis by Maser et al. checked the cost-effectiveness of using levofloxacin prophylaxis and analyzed the influence on quality-adjusted life-years (QALY). In this evaluation, the researchers compared the estimated cost of the levofloxacin prophylaxis to no prophylaxis in pediatric patients with relapsed ALL or AML receiving chemotherapy. They showed that levofloxacin prophylaxis effects cost savings. The estimated cost associated with the use of levofloxacin prophylaxis was lower vs. no antibiotic prophylaxis, and also a small profit in QALY was noticed. This analysis revealed a satisfactory cost/benefit ratio analyzing 99.2% of the iterations [3]. A summary of the main levofloxacin prophylaxis use results is set out in Table I below.

Ciprofloxacin prophylaxis

Ciprofloxacin is a second-generation class and one of the most-frequently used quinolones, obtained by a fluoridation of the quinolone structure [37]. This substance is also a broad-spectrum antibiotic, which shows the most potent activity against Gram-negative strains of all the fluoroquinolones [41]. In a single-center cohort study, Yeh et al. conducted a trial on 113 children with ALL and 36 with AML from January 2010 to December 2012. Patients received ciprofloxacin orally twice a day at a dose of 300 mg/m^2 in the case of neutropenia without fever, and when was expected more than seven days of neutropenia during intensive treatment. The research showed less frequent episodes of febrile neutropenia, and also a lower frequency of bacteremia during the ciprofloxacin prophylaxis period. There were 24 episodes of febrile neutropenia altogether in the ciprofloxacin prophylaxis period, compared to 96 episodes in the preprophylaxis period in a group of ALL patients. Similar results were obtained in AML patients. The authors also mentioned that this study was too short to draw any definite conclusions on any effect on the development of microbiological resistance [4].

In the Laoprasopwattana et al. [48] double-blind, randomized study of 95 patients (aged 0.25–18 years) with lymphoma and ALL, 45 of them received ciprofloxacin and 50 of them received a placebo therapy. The study was conducted from April 2007 to May 2010. Children were receiving either 20 mg/kg/day ciprofloxacin prophylaxis orally or a placebo. Additionally, rectal swab cultures were taken, to check if the applied antibiotic had an influence on increasing resistance. Prophylaxis was started within five days after the first day of chemotherapy, and lasted until the fever had increased to more than 38.5°C once or to 38°C twice or until adverse effects of ciprofloxacin were present, such as rash, arthropathy or when the patient had an absolute neutrophil count of 1,000/μL after two weeks of applied treatment. A significant difference was observed in the proportion of those who developed fever (50% in the ciprofloxacin group vs. 73% in the placebo group) in patients who underwent induction prophylaxis, but not consolidation (in the whole group of 71 patients who had been diagnosed with neutropenia). Regarding negative side effects, both groups of patients developed similar adverse effects related to the underlying disease (arthritis) and caused by chemotherapy-related nausea. One patient developed a maculopapular rash after the first day of ciprofloxacin treatment that was directly linked to the administration of the antibiotic. More importantly, in all three cases of bacteremia, the causative strains were sensitive to ciprofloxacin [48].

In a further single-center retrospective study conducted between October 2002 and October 2008, 103 patients with AML were divided into groups and received cefepime or vancomycin, oral ciprofloxacin, cephalosporin, or cefepime with ciprofloxacin administered orally at a dose of 250 mg/m^2 twice a day. A control group received only oral cephalosporin or no prophylaxis. The average age at diagnosis was 8.7 years. The main positive effect of prophylaxis was a reduction in infection episodes and a lower frequency of bacteremia caused by *S. viridans* but without a significant effect on the occurrence of febrile neutropenia [7]. In one of the American studies, 45 pediatric patients with de novo and relapsed AML (35 vs. 10) were enrolled. The patients were treated using ciprofloxacin prophylaxis. Patients were infused with ciprofloxacin intravenously at a dose of 15 mg/kg twice daily in every chemotherapy cycle. The control group underwent no prophylaxis. The authors observed a reduction in bacteremia caused by Gram-negative strains (13.4% with no prophylaxis vs. 4.7% with ciprofloxacin prophylaxis), with no change in the

Table I. Comparison of efficacy of levofloxacin, ciprofloxacin and moxifloxacin prophylaxis in patients with acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML)

Antibiotic prophylaxis	Number of patients	Age range [years]	Type of leukemia	Article type	Main results	References
Levofloxacin	344	3–11.9	ALL	Retrospective cohort study	Decreased episodes of fever, enterocolitis, bacteremia	Wolf et al. 2017 [22]
Levofloxacin, moxifloxacin	230	1–21	ALL	Randomized study	Bacteremia reduction, especially caused by Gram-negative strains strains	Sulis et al. 2018 [38]
Levofloxacin	200	3–16	AML, ALL	Randomized study	Lower risk of bacteremia, neutropenia and fever	Alexander et al. 2018 [27]
Levofloxacin	135	0.5–21	AML, ALL	Retrospective cohort study	Lower bacteremia caused by Gram--negative microorganisms	Davis et al. 2022 [39]
Ciprofloxacin	149	0.2–18	ALL, AML	Single-center cohort study	Less frequent episodes of febrile neutropenia, lower frequency of bacteremia	Yeh et al. 2014 [42]
Ciprofloxacin	140	0.25–18	ALL	Double-blind, randomized study	Lower frequency of fever episodes	Laoprasopwattana et al. 2013 [48]
Ciprofloxacin	103	<1–21	AML	Single-center retrospective study	Reduction in infections and lower frequency of bacteremia caused by *Streptococcus viridans*, but with no significant effect on occurrence of febrile neutropenia	Inaba et al. 2014 [7]
Ciprofloxacin	45	3.3–15.4	AML	Retrospective observational study	Reduction in bacteremia caused by Gram-negative strains	Felsenstein et al. 2014 [43]
Ciprofloxacin	69	0–13	ALL	Retrospective study	Lower frequency of bacteremia, especially Gram-negative strains	Yousef et al. 2004 [44]
Moxifloxacin, levofloxacin	85	≥18	AML, ALL	Single-center cohort study	Similar numbers of neutropenia episodes in both types of prophylaxis, higher rates of Gram-negative infections in moxifloxacin group than in levofloxacin	Lee et al. 2018 [47]

frequency of febrile neutropenia, the number of infectious episodes and mortality. The authors suggested that this substance, as a supportive care component, should be further investigated [43]. Another retrospective study was conducted on 69 patients with newly diagnosed acute lymphoblastic leukemia at the age of 0–13 who received ciprofloxacin prophylaxis during delayed intensification. The study was conducted between 1997 and 2000 and the patients received 25 mg/kg of ciprofloxacin twice a day. The patients were receiving antibiotic prophylaxis during delayed intensification no. 1 (5 week of chemotherapy), no. 2 (20 week) and no. 3 (35–42 weeks). The patients were receiving antibiotic prophylaxis during delayed intensification no. 1 (5 week of chemotherapy), no. 2 (20 week) and no. 3 (35–42 weeks). An oral antibiotic was given for 9.21 days (mean) in delayed intensification no. 1 and no. 2. In no. 3 ciprofloxacin prophylaxis was administered for 28 days. Ciprofloxacin prophylaxis reduced duration of hospitalization in no. 1 and no. 2 while in no. 3 both the rate and duration of hospitalization were reduced. A lower frequency of bacteremia was noted especially considering Gram-negative strains [44]. A summary of the main ciprofloxacin prophylaxis use results is set out in Table I.

Moxifloxacin prophylaxis

The fourth-generation of quinolones class consists of moxifloxacin. Compared to levofloxacin and ciprofloxacin antibiotics, moxifloxacin is a rarely used fluoroquinolone, but is more potent against anaerobic and Gram-positive bacteria [45, 46]. A few studies have shown the benefits of moxifloxacin prophylaxis use during leukemia treatment in adult patients, as described by Lee et al. [47], who in

a single-center cohort analysis enrolled 85 patients with ALL and AML (16 vs. 69), mostly during the induction phase, who received moxifloxacin (40 patients) or levofloxacin (45 patients) prophylaxis. Patients aged 18 and older were included in the trial from July 2012 to October 2014 and they received 500 mg/day of levofloxacin or 400 mg/day of moxifloxacin. The authors focused on the frequency of febrile neutropenia cases, number of infections and infection-related mortality, when comparing the use of moxifloxacin to levofloxacin. Among the moxifloxacin group, 22 patients experienced neutropenia episodes compared to 30 patients within the levofloxacin group, which suggested similar frequency rates of febrile neutropenia. Furthermore, the duration of neutropenia ≥10 days was a high-risk factor for febrile neutropenia despite the use of fluoroquinolone prophylaxis. However, no differences in the frequency of infections or the mortality rate were noted in both groups in the hospital. The authors observed higher rates of Gram-negative infections in the moxifloxacin group (25% vs. 10%) than the levofloxacin group [47]. A summary of the main moxifloxacin prophylaxis use results is set out in Table I.

Conclusions

The main challenge during leukemia treatment is an increased risk of infection incidents, mainly bacterial, which can lead to treatment failure. Several studies have shown that the prophylactic use of fluoroquinolones reduces bacteremia episodes during the treatment of ALL and AML in children. Despite potential negative side effects and antibiotic resistance related to fluoroquinolone prophylaxis, numerous benefits appear to outweigh the disadvantages. For this reason, it may be used as a potent treatment agent in the future and be introduced to the standard treatment of ALL and AML. Larger, randomized trials are needed to confirm the long-term effectiveness of these antibiotics.

Authors' contributions

JZ, ML — conceptualization. JZ, NZ, WM — methodology. NZ, WM, ML — writing, original draft preparation. JZ, ML — review and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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