SHORT COMMUNICATION

Prophylactic use of Levofloxacin during induction of acute lymphoblastic leukaemia in children—experience from Pakistan

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Abstract

To assess whether prophylactic use of Levofloxacin would reduce the number of febrile neutropenia episodes during the induction phase, a single-centre, case-control study was carried out. Data was collected prospectively of patients who received Levofloxacin prophylaxis during the induction chemotherapy from September 2019 till October 2020. The cases were compared with historical controls who did not receive antibiotics prophylaxis. A total of 121 patients were enrolled, among which 61 patients were cases, whereas 60 patients were controls. The patients who received Levofloxacin prophylaxis had lower rate of febrile neutropenia episodes than patients who did not receive any prophylaxis ($p \leq 0.01$) (odds ratio [OR]:0.23, CI 95%). No significant difference in induction mortality was seen between the two groups ($p \leq 0.14$). Levofloxacin prophylaxis reduced the rate of febrile neutropenia episodes among patients, but it did not affect the infection related mortality.

Keywords: Antibiotic Prophylaxis, Acute Lymphoblastic Leukaemia, Children.

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Introduction

Acute leukaemia is the most common childhood malignancy. Over the years the outcomes of acute lymphoblastic leukaemia have dramatically improved due to the introduction of response-based therapy.[1] Infectious complications are commonly seen during the induction phase of acute lymphoid and myeloid leukaemia as the intensive chemotherapy regimen leads to prolonged neutropenia and there is high risk of bacterial and fungal sepsis. Chemotherapy along with high dose dexamethasone during the induction phase and poor nutritional status are factors leading to it.[2] In low-middle income countries infectious complications are the most common cause of treatment-related morbidity and mortality, resulting in induction mortality of 8-10%.[3]

Antibiotic prophylaxis has long been considered among patients diagnosed with acute myeloid leukaemia on intensive chemotherapy regimens in the neutropenic phase, as it can reduce febrile neutropenia episodes and its complications.[4] Sulis et al reported a lower prevalence of febrile neutropenia episodes and bacteraemia when prophylaxis was used (10.9% vs. 24.4%, $p<0.0001$).[5]

There is a lack of consensus due to questions about the extent of benefit of antibiotic prophylaxis and the concern of emergence of resistant organisms.

This study was conducted to assess whether prophylactic use of Levofloxacin would reduce the number of episodes of febrile neutropenia and its complications during the induction phase of therapy in comparison with historical controls.

Material and Methods

A pilot study was conducted from September 2019 till October 2020 at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore. The study was approved by the hospital's Institutional Review Board (IRB-19-09). Informed written consent was obtained from each patient's parent or guardian prior to enrolment. Data was collected prospectively from the electronic medical record. Patients' between 2-5 years of age diagnosed with acute lymphoblastic leukaemia were enrolled. Patients who had clinically or microbiologically documented infection before starting induction therapy were excluded from the study. Patients afebrile on presentation were started on Levofloxacin primary prophylaxis (10 mg per kg twice daily dose).[6] Those who had fever on presentation without evidence of microbiologically documented infection were started on antibiotics as per institutional guidelines, and were switched to Levofloxacin prophylaxis after resolution of fever (approximately 24-48 hours after initiation of therapy). Levofloxacin was given in the post induction period until the resolution of neutropenia. Historical controls from August 2018 till August 2019 who met the same criteria as cases were considered for comparison. Both the groups received Trimethroprim-Sulfamethaxazole (Co-trimoxazole) prophylaxis against pneumocystis

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Jirovecii pneumonia. Induction chemotherapy was based on National Cancer Institute (NCI) risk assessment.[7]

The primary end points of the study were: number of febrile neutropenia episodes, time to the first episode of febrile neutropenia in days, total number of days of admission due to febrile neutropenia, and episodes of blood stream infections. The secondary end point was overall survival at the end of induction.

Infectious events: For all infection related events, the common terminology criteria for adverse events (CTAE) v 4.0 was used. Febrile neutropenia was defined as a disorder characterised by an ANC <1000/mm^3 and a one time temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour. Sepsis was defined as a disorder characterised by the presence of pathogenic micro-organisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock.[8] Infection related admission in hospital days was counted for both groups (cases and controls). Further stratification of infectious events was based as per the standard definitions (Table 1).[9,10]

Statistical Analysis: The IBM SPSS version 20 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Quantitative variables were presented as median/mean (range: minimum maximum/standard deviation), and qualitative variables were presented by frequencies and percentages. The independent t-test, Mann-Whitney U test, Chi-square test, and Fisher's exact test were applied to analyse the differences between the two groups according to the type of data. Univariable logistic regression model was used to assess the relationship between Levofloxacin prophylaxis and febrile neutropenia. The tests used were all two-sided with less than 5% type I error. The differences between the groups were significant p<0·05.

Results

From September 2019 till October 2020, a total 61 patients (cases group) diagnosed with ALL at Shaukat Khanum Memorial Cancer hospital and Research Centre were enrolled in this prospective study.

Sixty patients from August 2018 till August 2019 who did not receive Levofloxacin prophylaxis were taken as historical controls (control group).

The mean age of presentation of both groups was 3.3 years, no significant difference was seen in clinical characteristics (Table 2).

Table-2: Characteristics of Patients with and without Levofloxacin Prophylaxis.

Characteristic	Levofloxacin Prophylaxis (n=61)	No Prophylaxis (n=60)	p value
Age (years)			
Gender			
Male	34	30	0.32
Female	27	30	
Immunophenotyping			
B cell	59	54	0.13
T cell	2	6	
White cell count			
< 50k	54	48	0.04
>50k	7	6	
Induction Regimen			
3 drugs	47	46	0.56
4 drugs	14	14	
Fever on presentation			
Yes	30	41	0.025
No	31	19	
MRD at end Induction			
Negative	49	36	0.15
Positive	8	2	
Status at end Induction			
Alive	57	51	0.14
Dead	4	9	

Table-1: Standard Definitions.

Outcomes	Definition
Profound neutropenia	Absolute neutrophil count <200/ul
Bacteraemia	A recognised organism cultured from one or more blood cultures,[10]
Clinically documented infection	Site of infection that is diagnosed but its microbiological pathogenesis is not determined or is clinically inaccessible,[10]
Microbiologically documented infection	Infection is clinically and microbiological detectable, with supportive evidence positive culture, antigen or PCR test results, or characteristic histopathological findings.[10]
ICU admission	Requirement for ICU, HDU or other critical care unit for organ support including cardiovascular, respiratory, neurological, haematological, renal or hepatic.[10]
Invasive fungal infection[a]	Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by fine needle aspiration or biopsy from a sterile site, or Blood culture that yields yeast (e.g., Cryptococcus or Candida species) or yeast-like fungi (e.g., Trichosporon species).[11]
Invasive Probable fungal infection	Radiological findings favouring fungal infection in the context of febrile neutropenia, positivity of fungal markers, Galactomannan antigen and Beta D Glucan detected in plasma .[11]

Thirty (49%) patients out of 61 who were started on Levofloxacin prophylaxis had fever on presentation, which was stratified as disease fever and resolved within 24 hours after initiation of chemotherapy.

The patients who received Levofloxacin prophylaxis had fewer episodes of febrile neutropenia, total 37(42.5%) compared to the patients who did not receive any prophylaxis, 50 episodes (57.5%) (p≤ 0.005)

Table-3: Organisms isolated.

Infection	Levofloxacin Prophylaxis (n)	No Prophylaxis (n)	*p*-value
Bacterial			0.39
Gram Positive bacteraemia			
Strep. viridians	1		
VRE[a]	1	1	
MRSA[b]		4	
Gram Negative bacteraemia			
Pseudomonas	1	4	
E-Coli[c]	2	2	
MDR E-Coli[d]	4	4	
Fungal Isolates			0.66
Candida famata	1		
Candida Tropicalis	1		
Candida Albicans	1		
Aspergillus fumigatus	2	3	
Aspergillus flavus	1	1	
Mucormycosis*		1	

[a] vancomycin resistant enterococcus, [b] Methicillin resistant staphylococcus aureus, [c] Escherichia Coli, [d] MDR- E-coli strains were resistant to all anti-biotics except Colistin; Invasive mucormycosis infection was seen in one patient with no prophylaxis, who developed intestinal obstruction resulting in necrotic bowel, resection of the necrotic segment revealed invasive fungal infection.

(odds ratio [OR] :0.30 (0.13-0.72), CI 95%).

The duration in days, from the start of therapy to first episode of febrile neutropenia was slightly reduced in the group which received Levofloxacin prophylaxis, median 7 days (range 1-30 days) compared to the control group who did not receive any prophylaxis median 3 days (range 1-21 days). The control group experienced more episodes of febrile neutropenia as compared to the group which received Levofloxacin prophylaxis ($p \leq 0.05$) (Figure 2).

The patients who received no antibiotic prophylaxis had slightly prolonged hospital admission due to febrile neutropenia episodes (median 7 [1-35] days) as compared to those who received levofloxacin prophylaxis (median 5 [1-27] days) $p \leq 0.04$.

In all 26 episodes of blood stream infections (BSI) were noted between the two groups. Invasive fungal disease was seen in 11 patients among the two groups. MRSA infections were seen in the group which did not receive any prophylaxis. (Table 3).

The number of days of antibiotic exposure slightly differed between the two groups; the mean number of days of Piperacillin/Tazobactam exposure in the group that received Levofloxacin was 6.6±4.5 days, whereas in patients who received no prophylaxis it was 7.8±3.4 days (p=0.81). The number of days of Meropenem, Vancomycin, Colistin, and Amphotericin in patients who received Levofloxacin prophylaxis were 9.4±4.7 days, 6.0±3.0 days, 6.0±3.0 days, and 8.0±3.8 days, respectively. Whereas the number of days of Meropenem, Vancomycin, Colistin, and Amphotericin in patients who received no prophylaxis were 7.2±3.5 days, 7.6±3.9 days, 9.5±6.3 days, and 8.3±6.1 days (Figure 1).

Intensive care admission was seen in 15 patients, among which 6 patients received Levofloxacin prophylaxis with mean ICU stay of 6.67±5.27days, whereas 9 patients received no prophylaxis with mean ICU stay 5.22±2.63 days ($p \leq 0.49$).

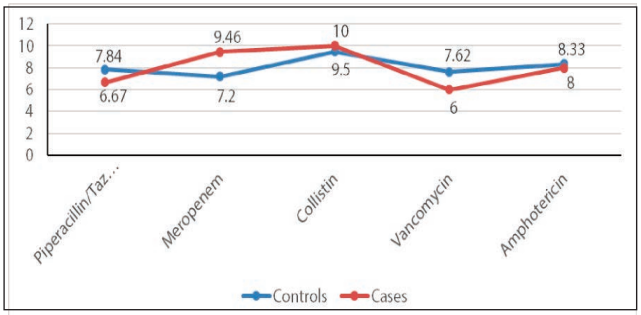

Figure-1: IMean days of antibiotic exposure among cases and controls.

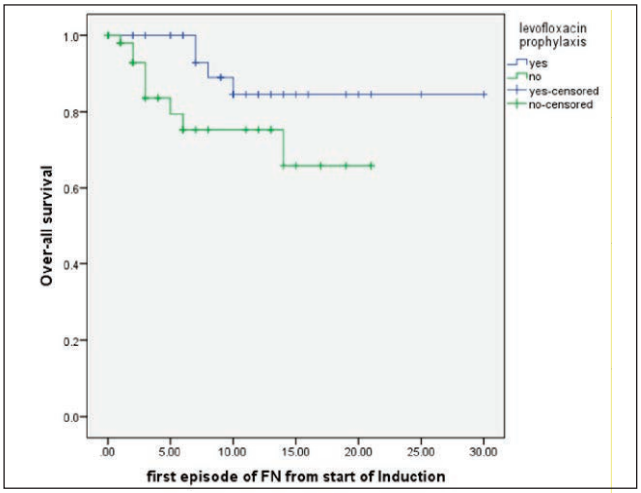

Figure-2: First episode of Febrile neutropenia among cases and controls.

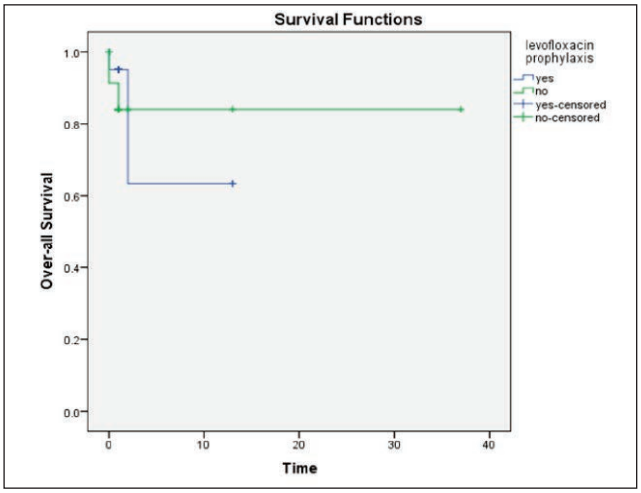

Figure-3: Over-all survival among the cases and controls group.

Among the group which received Levofloxacin prophylaxis, 4 (6.5%) patients died at the end of induction from infection-related complications compared to 9 (15%) patients who received no prophylaxis. The over-all survival at the end of induction among the group who received Levofloxacin prophylaxis was 93.4% and the group who received no prophylaxis was 84.5% ($p \leq 0.14$) (Figure 2). The event-free survival at the end of induction in relation to the first episode of febrile neutropenia was 92.2% in the group which received Levofloxacin and 83.6% in group which received no prophylaxis ($p \leq 0.05$) (Figure 3).

Conclusion

Levofloxacin prophylaxis reduced the febrile neutropenia episodes among our patient population, but it did not affect the infection-related mortality. Further studies regarding antibiotic prophylaxis need to be carried out to determine the risk of multi-dug resistant organisms over time.

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Conflict of Interest: The authors declare no conflict of interest.

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