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ORIGINAL RESEARCH

Randomized double blind trial of ciprofloxacin prophylaxis during induction treatment in childhood acute lymphoblastic leukemia in the WK-ALL protocol in Indonesia

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Objectives: Toxic death is a big problem in the treatment of childhood acute lymphoblastic leukemia (ALL), especially in low-income countries. Studies of ciprofloxacin as single agent prophylaxis vary widely in success rate. We conducted a double-blind, randomized study to test the effects of ciprofloxacin monotherapy as prophylaxis for sepsis and death in induction treatment of the Indonesian childhood ALL protocol.

Methods: Patients were randomized to the ciprofloxacin arm (n = 58) and to the placebo arm (n = 52). Oral ciprofloxacin monotherapy or oral placebo was administered twice a day. All events during induction were recorded: toxic death, abandonment, resistant disease, and complete remission rate.

Results: Of 110 patients enrolled in this study, 79 (71.8%) achieved CR. In comparison to the placebo arm, the ciprofloxacin arm had lower nadir of absolute neutrophil count during induction with median of 62 (range: 5–884) versus 270 (range: 14–25,480) $\times 10^9$ cells/L ($P < 0.01$), greater risks for experiencing fever (50.0% versus 32.7%, $P = 0.07$), clinical sepsis (50.0% versus 38.5%, $P = 0.22$), and death (18.9% versus 5.8%, $P = 0.05$).

Conclusion: In our setting, a reduced intensity protocol in a low-income situation, the data warn against using ciprofloxacin prophylaxis during induction treatment. A lower nadir of neutrophil count and higher mortality were found in the ciprofloxacin group.

Keywords: ciprofloxacin, prophylaxis, childhood acute lymphoblastic leukemia, randomized trial, low-income country

Introduction

Childhood acute lymphoblastic leukemia (ALL) patients may experience immunosuppression, either due to the disease or as a result of chemotherapy, or both. This condition occurs particularly during induction and re-induction phases, in which intensive treatment is conducted.[1–3] It may lead to fatal infections, especially if the patients are malnourished and if there is lack of access to supportive care. Previous studies have shown that prophylactic antimicrobial treatment can reduce infection-related morbidity and mortality after oral or intravenous administration.[4–9]

Contrary to the setting in high-income countries, poverty, malnutrition, and the generally poor clinical condition of patients, as well as poor access to supportive care in low- to middle-income countries, have generated a higher incidence of treatment-related mortality and lower remission rates. A study in Dr Sardjito Hospital, Yogyakarta, Indonesia, as reported by Mostert et al,[10] revealed that between 1997 and 2002 the

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toxic death rate was an obvious problem; approximately 23% of patients experienced treatment-related death and 35% refused or abandoned treatment. The majority of these events occurred during induction. Both events result in low remission and cure rates in our hospital setting.

We therefore conducted this randomized, double-blind study to test the role of ciprofloxacin oral monotherapy as prophylaxis for bacterial infection and toxic death during induction treatment of Indonesian childhood ALL protocol.

Patients and methods

Patients

The study groups consisted of children with ALL hospitalized in Dr Sardjito Hospital, Yogyakarta, Indonesia from July 1999 until June 2005, who met the inclusion criteria as follows: diagnosis of ALL based on French–American–British morphology classification of L1 or L2;[11] and age between 0 and 14 completed years during induction treatment for the standard risk (SR) and high risk (HR) groups of the Indonesian Wijaya Kusuma (WK)-ALL-2000 protocol. Patients were defined as SR when their age at diagnosis was between 1 year and 9 completed years; their WBC count was less than 50×10^9/L; and there was an absence of mediastinal mass and no signs of central nervous system (CNS) involvement. Patients who did not meet SR criteria were assigned as HR. SR patients with a day 8 absolute peripheral lymphoblasts count 1×10^9/L or higher were upgraded to the HR group and treated accordingly. Fever was defined as an axillary temperature $\geq$ 38.5°C in a single determination or >38°C after two measurements with a 1-hour interval between each measurement. Clinical sepsis was defined when there was fever plus documented clinical signs and symptoms of systemic infection with or without increasing C-reactive protein level. Microbiological studies and surveillance were not always done for financial reasons.

The exclusion criteria were known allergy to quinolones, epilepsy, and/or body weight (BW) less than 10 kg. Patients were classified as undernourished at diagnosis when Z-score value was –2 SD or less based on weight-for-age (0–5 years) and height-for-age (5–15 years) World Health Organization standards for nutritional status.[12,13]

The WK-ALL-2000 protocol

The WK-ALL-2000 protocol for childhood ALL was developed in 1998–1999 as a relatively economical, reduced-intensity protocol to meet conditions in Indonesia after the Asian economical crisis.[14] The protocol includes a 6-week induction treatment of three doses of weekly age-adjusted intrathecal methotrexate administered in weeks 0, 2, and 6; daily oral dexamethasone 6 mg/m^2 for 42 days; five doses of weekly intravenous vincristine 1.5 mg/m^2 during weeks 1–5; and two doses of intravenous *Escherichia coli* L-asparaginase 6000 IU/m^2 in weeks 1 and 2 for SR or weeks 4 and 5 for HR patients. One dose of intravenous daunorubicin 30 mg/m^2 was added at week 1 for HR patients only. HR patients also received a re-induction schedule inserted between the consolidation and maintenance phase. The scheme of the protocol is shown in Table 1.

Random assignment

Patients were randomized using a computer into arm A and arm B. Arm A had tablets containing ciprofloxacin prepared in the pharmacy, while the placebo tablet contained tasteless material. Both the patients and the doctors and other staff were blinded to the tablet contents, and the groups were not unblinded until after the inclusion period had ended.

The tablets were taken orally twice per day from the onset of chemotherapy administration. The ciprofloxacin doses depended on the patient's BW: BW 10–14 kg = 2 × 125 mg; BW 15–24 kg = 2 × 250 mg; BW 25–39 kg = 2 × 500 mg; and BW 40 kg or more = 2 × 750 mg. The tablets were taken continuously at home when the patient was discharged from hospital until completion of induction treatment. Modification of this treatment was permitted if the patient had fever.

Statistical analysis

The data were collected in a research-patient file and transferred to a computer spreadsheet form containing information of the protocol used, presentation at diagnosis (sex, age group, WBC group, risk group, nutritional status), day 8 peripheral lymphoblasts count, any fever and clinical sepsis, date of death or abandonment, and remission status at the end of the induction treatment.

The protocol stated day 43 as the end of induction treatment and remission determination. Patients achieved complete remission when their lymphoblast count in bone marrow was less than 5% without any signs of leukemic infiltration in peripheral blood, cerebrospinal fluid, or other organs. Abandonment of treatment, death, and no remission achievement were classified as induction failures.

The outcomes measured in this study were fever, clinical sepsis and mortality. The analysis was carried out using SPSS software (v13; IBM Corporation, Armonk, NY) and statistical significance was defined at the two-sided P-value < 0.05.

Table 1 Induction treatment of WK-ALL-2000 protocol.[14]

Medicine	Schedule of administration
Methotrexate, ith	Days 1, 15, 42
Dexamethasone 6 mg/m^2, po	Days 1–42
Vincristine 1.5 mg/m^2, iv	Days 8, 15, 22, 29, 36
L-asparaginase 6.000 U/m^2, iv	Days 8, 15 (standard-risk patients) or Days 29, 36 (high-risk patients)
Daunorubicin 30 mg/m^2, iv	Day 8 (high-risk patients only)

Notes: The dose of ith methotrexate was adjusted to age: <1 year = 6 mg; 1–2 years = 8 mg; 2–3 years = 10 mg; ≥ 3 years = 12 mg. The dose of oral dexamethasone was tapered-on during the first week when the initial WBC count was >20 × 10^9/L and tapered-off during the sixth week in all patients. Bone marrow aspirations were done on day 0 for diagnosis and at the end of induction treatment to determine remission achievement.
Abbreviations: ith, intrathecal; po, per oral; iv, intravenous; WK-ALL-2000, Wijaya Kusuma acute lymphoblastic leukemia protocol.

Results

One-hundred and ten patients were enrolled in this study and randomized into arm A (58 patients or 53%) and arm B (52 patients or 47%). The characteristics of patients were not equally divided between the two groups as shown in Table 2. The ciprofloxacin group was less often under-nourished than the placebo group (24.1% vs 44.2%, $P = 0.03$).

Of the 110 patients, 79 (71.8%) achieved complete remission. Adverse outcomes during induction treatment were dominated by death (12.8%) and abandonment (9.0%). The remaining patients (6.4%) had resistant disease. Patients in the ciprofloxacin arm have a greater induction failure rate (31.0% vs 25.0%; 95% CI: 0.58–3.12; $P = 0.48$; Table 3), more fever (50.0% vs 32.7%; 95% CI: 0.95–4.47; $P = 0.07$), more clinical sepsis (50.0% vs 38.5%; 95% CI: 0.75–3.42; $P = 0.22$), and more toxic death (18.9% vs 5.8%; 95% CI: 0.92–13.80; $P = 0.05$). However, these results were not statistically significant. Twelve of 14 induction deaths occurred in the hospital; six of these were infective death, due to sepsis (five patients) and varicella (one patient) as shown in Table 4. However, the patients diagnosed with disseminated intravascular coagulation, multiorgan dysfunction syndrome, and shock may well have had infection as the causative event. The nadir of the absolute neutrophil count during induction in the ciprofloxacin arm was lower than in the placebo arm (median 62 [range: 5–884] vs 270 [range: 14–25,480] cells/μl; $P < 0.01$). The ciprofloxacin arm and the placebo arm had an equal induction duration (median 43 [range: 40–58] vs 43 [range: 39–59] days, respectively).

Table 5 shows that there was no significant difference in the incidence of diarrhea, nausea, vomiting, and neuritis as adverse events during induction between the ciprofloxacin arm and placebo arm. The characteristics and clinical outcome during induction treatment of each patient is shown in Table 6.

Discussion

Deaths, whether related to the disease itself or chemotherapy-induced, are common in leukemia treatment. The toxic death rate (23%) together with treatment refusal or abandonment of treatment (35%) are big problems in Dr Sardjito Hospital.[10]

Table 2 Characteristics of patients

Characteristics	Placebo		Ciprofloxacin		Total		*P*-value
	n	%	n	%	n	%	
Total patients	52	47.3	58	52.7	110	100	
Sex							
Male	34	65.4	37	60.3	69	62.7	0.86
Female	18	34.6	21	39.7	41	37.3	
Age group (years)							
1–9	40	76.9	49	84.5	89	80.9	0.31
10–14	12	23.1	9	15.5	21	19.1	
WBC at diagnosis (×10^9/L)							
<50	37	71.2	43	74.1	80	72.7	0.73
≥50	15	28.8	15	25.9	30	27.3	
Risk group							
Standard risk	27	51.9	32	55.2	59	53.6	0.73
High risk	25	48.1	26	44.8	51	46.4	
Nutritional status							
Well-nourished	29	55.8	44	75.9	73	66.4	0.03
Undernourished	23	44.2	14	24.1	37	33.6	
Day 8 absolute peripheral lymphoblasts count (×10^9/L)[a]							
<1	40	80.0	44	80.0	84	80.0	1.00
≥1	10	20.0	11	20.0	21	20.0	

Note: [a]Data were not available in five patients due to death or abandonment of treatment before measurement (n = 3 in ciprofloxacin group, n = 2 in placebo group).
Abbreviation: WBC, white blood cell.

Table 3 Outcomes during induction treatment

Outcomes	Placebo		Ciprofloxacin		Total		OR	95% CI	*P*-value
	n	%	n	%	n	%			
Total patients	52	47.3	58	52.7	110	100			
Induction outcome									
Complete remission	39	75.0	40	69.0	79	71.8			
Induction failures	13	25.0	18	31.0	31	28.2	1.35[a]	0.58–3.12	0.48[#]
Death	3	5.8	11	18.9	14	12.8	3.57[a]	0.92–13.80	0.05[#]
Abandonment	7	13.5	3	5.2	10	9.0	0.42[a]	0.10–1.73	0.32[##]
Resistant disease	3	5.8	4	6.9	7	6.4	1.3[a]	0.27–6.19	1.00[##]
Fever > 38.5°C									
Never	35	67.3	29	50.0	64	58.2			
Ever	17	32.7	29	50.0	46	41.8	2.06[b]	0.95–4.47	0.07[#]
Clinical sepsis									
Never	32	61.5	29	50.0	61	55.5			
Ever	20	38.5	29	50.0	49	44.5	1.60[b]	0.75–3.42	0.22[#]

Notes: [a]ORs for any induction failure and specific induction failures (CR is taken as the reference outcome category); [b]ORs for event of fever and clinical sepsis (Never is taken as the reference outcome category); [#]Chi-square test; [##]Fisher's exact test.
Abbreviations: OR, odds ratio (ciprofloxacin group relative to placebo group); CI, confidence interval.

These kinds of problems are typically found in resource-poor countries with poor and malnourished patients, poor access to supportive care, and lack of access to medicines.[15–17] The condition is contrary to that in high-income countries where toxic death rates are generally much fewer (2%–4%) and abandonment is virtually unknown.[18,19] An important underlying cause of a high toxic death rate in childhood ALL is neutropenia, which may be found at diagnosis as a consequence of the leukemia itself, or following chemotherapy. Infections in individuals with neutropenia can develop into a life threatening condition and therefore require prompt intervention. Initiation of empiric antibiotics immediately after the neutropenic cancer patient becomes febrile has been the single most important advance in the management efforts to diminish mortality rates in the immunocompromized host.[20] Unfortunately, trials to decrease the infection-related mortality in neutropenic patients utilizing antibacterial prophylaxis and the use of hematopoietic growth-stimulating factors have shown conflicting results.[8,21–24] In terms of primary antibiotic prophylaxis, ciprofloxacin or quinolone derivates have been widely used because they show wide antibacterial spectrum activity, mainly against Gram-negative bacteria from the gut, where invasive bacteria for systemic infection originate. Another benefit of quinolones, besides their effectiveness, is that they are generally well-tolerated and can be administered orally.[7,25,26] Based on such findings, and because it is available at low-cost in our setting, we used ciprofloxacin in our study. We hypothesized that prophylactic ciprofloxacin administration would diminish infection and mortality during induction, thus increasing the remission and cure rates of childhood ALL in our hospital setting.

Some unexpected results were obtained in our study. First of all, the randomization was not balanced for malnutrition, and the ciprofloxacin group had the lower percentage of malnourished patients. It is clear that malnutrition is an important factor for fever and infection; nevertheless, patients in the ciprofloxacin arm showed a higher risk of developing fever, clinical sepsis, and death from complications than patients in the placebo arm. Therefore, we checked whether the groups had not been accidentally exchanged, but this was not the

Table 4 Cause of death during induction treatment

Causes of death	Placebo		Ciprofloxacin		Total	
	n	%	n	%	n	%
Total patients	3	11.4	11	78.6	14	100
Sepsis	3	5.8	2	3.4	5	35.7
Varicella	0	0	1	1.7	1	7.1
Intracranial hemorrhage	0	0	2	3.4	2	14.2
DIC	0	0	1	1.7	1	7.1
MODS	0	0	1	1.7	1	7.1
Hypovolemic shock	0	0	1	1.7	1	7.1
Transfusion reaction	0	0	1	1.7	1	7.1
No data or died at home	0	0	2	3.4	2	14.2

Abbreviations: DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome.

Table 5 Adverse events during induction treatment

Events	Placebo		Ciprofloxacin		Total	
	n	%	n	%	n	%
Total patients	52	47.3	58	52.7	110	100
Nausea	8	15.4	3	5.2	11	10.0
Vomiting	7	13.5	6	10.3	13	11.8
Diarrhea	2	3.8	4	6.9	6	5.5
Neuritis	7	13.5	5	8.6	12	11.0

Table 6 Presentation at diagnosis and clinical outcome

Patient	Random	Sex	Age (years, months)	WBC count (/μl)	Risk group	Nutritional state	Day 8 response (/μl)	Induction outcome	Cause of death	Fever	Sepsis
1	Cip	M	7, 02	<50,000	SR	Well	<1000	CR		Ever	Never
2	Pcb	F	5, 05	≥50,000	HR	Well	<1000	CR		Never	Never
3	Pcb	F	5, 01	<50,000	SR	Well	≥1000	CR		Never	Never
4	Cip	F	3, 04	<50,000	SR	Well	<1000	CR		Ever	Ever
5	Cip	M	10, 00	≥50,000	HR	Well	<1000	CR		Never	Never
6	Cip	F	10, 00	≥50,000	HR	Under	<1000	RD		Ever	Never
7	Pcb	M	1, 00	≥50,000	HR	Under	≥1000	CR		Ever	Ever
8	Cip	M	4, 01	≥50,000	HR	Well	≥1000	Death	Disseminated intravascular coagulation	Ever	Never
9	Pcb	M	14, 01	≥50,000	HR	Under	≥1000	Death	Sepsis	Ever	Ever
10	Cip	M	4, 04	≥50,000	HR	Well	<1000	Death	Sepsis	Ever	Ever
11	Pcb	M	7, 03	≥50,000	HR	Under	<1000	Death	Sepsis	Never	Never
12	Cip	F	5, 11	≥50,000	HR	Well	≥1000	CR		Ever	Ever
13	Cip	M	2, 07	<50,000	SR	Under	<1000	CR		Ever	Ever
14	Cip	F	14, 01	≥50,000	HR	Well	≥1000	CR		Ever	Never
15	Cip	M	8, 06	<50,000	SR	Under	<1000	CR		Ever	Ever
16	Cip	F	1, 08	<50,000	SR	Well	<1000	CR		Never	Ever
17	Pcb	M	2, 06	<50,000	SR	Well	<1000	CR		Ever	Ever
18	Pcb	M	13, 00	<50,000	HR	Under	<1000	CR		Never	Ever
19	Cip	M	1, 10	<50,000	HR	Well	<1000	CR		Never	Ever
20	Pcb	M	2, 05	≥50,000	HR	Well	<1000	CR		Never	Never
21	Pcb	M	13, 01	<50,000	HR	Well	<1000	CR		Never	Never
22	Pcb	F	9, 09	<50,000	SR	Well	<1000	CR		Ever	Never
23	Pcb	F	6, 06	<50,000	SR	Well	<1000	CR		Ever	Ever
24	Cip	F	6, 07	<50,000	SR	Under	<1000	CR		Never	Never
25	Cip	M	2, 09	<50,000	SR	Well	<1000	CR		Never	Never
26	Pcb	M	8, 01	<50,000	SR	Well	<1000	CR		Never	Never
27	Cip	M	7, 05	<50,000	SR	Well	<1000	CR		Never	Ever
28	Cip	M	1, 08	≥50,000	HR	Well	<1000	CR		Ever	Ever
29	Pcb	M	6, 03	<50,000	SR	Under	<1000	CR		Never	Never
30	Cip	M	13, 00	≥50,000	HR	Well	≥1000	RD		Ever	Ever
31	Pcb	M	2, 01	<50,000	SR	Under	<1000	CR		Ever	Ever
32	Pcb	F	14, 00	≥50,000	HR	Under	≥1000	RD		Never	Never
33	Cip	F	1, 06	<50,000	SR	Well	<1000	CR		Never	Ever
34	Pcb	M	6, 06	<50,000	SR	Well	<1000	CR		Never	Ever
35	Cip	M	3, 03	<50,000	SR	Under	<1000	CR		Ever	Ever
36	Pcb	F	7, 08	<50,000	SR	Well	<1000	CR		Never	Never
37	Pcb	M	3, 03	<50,000	SR	Under	<1000	Abn		Never	Ever
38	Pcb	F	2, 11	<50,000	SR	Well	<1000	CR		Never	Never
39	Cip	M	5, 01	<50,000	SR	Well	<1000	CR		Ever	Never
40	Cip	M	3, 02	≥50,000	HR	Well	<1000	CR		Ever	Never
41	Pcb	M	4, 03	<50,000	SR	Well	<1000	CR		Ever	Ever
42	Pcb	M	6, 07	<50,000	SR	Well	<1000	CR		Never	Never
43	Cip	F	4, 00	<50,000	SR	Under	<1000	CR		Ever	Ever
44	Cip	M	14, 00	≥50,000	HR	Under	≥1000	Abn		Never	Ever
45	Pcb	M	4, 01	<50,000	SR	Well	<1000	CR		Never	Never
46	Pcb	M	1, 03	<50,000	SR	Well	<1000	Abn		Ever	Ever
47	Pcb	F	7, 07	<50,000	SR	Well	<1000	Abn		Never	Never
48	Pcb	M	12, 01	<50,000	HR	Under	No data	Abn		Never	Never
49	Pcb	M	4, 02	<50,000	SR	Under	<1000	CR		Ever	Ever
50	Cip	F	6, 05	<50,000	HR	Well	<1000	CR		Ever	Ever

(*Continued*)

Table 6 (*Continued*)

Patient	Random	Sex	Age (years, months)	WBC count (/μl)	Risk group	Nutritional state	Day 8 response (/μl)	Induction outcome	Cause of death	Fever	Sepsis
51	Cip	M	3, 04	<50,000	HR	Well	<1000	CR		Never	Never
52	Cip	F	11, 00	<50,000	HR	Under	<1000	Death	Sepsis	Ever	Ever
53	Pcb	M	4, 08	≥50,000	HR	Well	No data	Death	Sepsis	Ever	Ever
54	Cip	M	2, 05	<50,000	HR	Under	No data	Death	Multiple organs dysfunction	Ever	Ever
55	Pcb	M	5, 02	<50,000	SR	Under	<1000	CR		Ever	Never
56	Cip	F	8, 01	<50,000	SR	Well	<1000	CR		Never	Never
57	Cip	M	2, 08	<50,000	SR	Well	<1000	CR		Ever	Never
58	Cip	M	4, 09	<50,000	HR	Well	<1000	CR		Ever	Ever
59	Cip	M	9, 03	<50,000	SR	Under	<1000	RD		Ever	Never
60	Cip	F	9, 07	<50,000	SR	Well	<1000	Death	Hypovolemic shock	Ever	Ever
61	Cip	M	2, 09	<50,000	SR	Well	No data	Death	Intracranial hemorrhage	Ever	Ever
62	Pcb	F	5, 03	<50,000	SR	Well	<1000	CR		Never	Never
63	Pcb	F	5, 07	≥50,000	HR	Under	<1000	CR		Never	Ever
64	Cip	M	3, 04	<50,000	SR	Well	≥1000	CR		Never	Never
65	Cip	M	8, 09	<50,000	SR	Well	<1000	CR		Never	Ever
66	Cip	F	4, 08	<50,000	SR	Under	<1000	CR		Never	Never
67	Pcb	F	2, 09	<50,000	SR	Well	<1000	RD		Ever	Ever
68	Cip	F	2, 07	<50,000	SR	Well	≥1000	Death	No data	Never	Ever
69	Pcb	F	6, 09	<50,000	SR	Under	≥1000	CR		Never	Never
70	Cip	M	10, 00	≥50,000	HR	Well	<1000	CR		Never	Never
71	Pcb	M	8, 01	≥50,000	HR	Under	≥1000	Abn		Ever	Ever
72	Cip	M	3, 08	<50,000	SR	Well	≥1000	CR		Ever	Ever
73	Cip	M	5, 09	<50,000	HR	Under	<1000	CR		Never	Ever
74	Cip	M	4, 01	<50,000	SR	Well	No data	Abn		Never	Never
75	Cip	F	13, 00	<50,000	HR	Well	≥1000	Death	No data	Never	Never
76	Cip	M	2, 03	≥50,000	HR	Well	≥1000	RD		Ever	Ever
77	Pcb	M	12, 01	<50,000	HR	Well	<1000	CR		Never	Never
78	Pcb	M	8, 07	<50,000	SR	Under	<1000	CR		Never	Never
79	Cip	F	4, 05	<50,000	SR	Well	<1000	CR		Ever	Never
80	Pcb	M	2, 01	≥50,000	HR	Well	≥1000	CR		Never	Never
81	Pcb	M	7, 05	≥50,000	HR	Under	≥1000	Abn		Never	Ever
82	Pcb	M	11, 01	<50,000	HR	Under	<1000	CR		Never	Never
83	Pcb	M	14, 00	≥50,000	HR	Well	≥1000	CR		Never	Never
84	Cip	M	10, 00	<50,000	HR	Well	<1000	Death	Varicella	Never	Never
85	Cip	M	3, 08	<50,000	HR	Well	<1000	CR		Never	Never
86	Pcb	M	12, 00	<50,000	HR	Under	<1000	CR		Ever	Ever
87	Cip	F	2, 00	<50,000	SR	Well	<1000	CR		Never	Never
88	Cip	M	5, 09	≥50,000	HR	Well	<1000	Death	Transfusion reaction	Never	Never
89	Cip	M	4, 04	<50,000	SR	Well	<1000	CR		Never	Never
90	Pcb	M	14, 01	≥50,000	HR	Under	<1000	CR		Ever	Never
91	Pcb	M	5, 05	<50,000	SR	Well	<1000	CR		Never	Never
92	Pcb	M	2, 00	<50,000	SR	Well	<1000	RD		Never	Never
93	Cip	M	3, 00	<50,000	SR	Well	<1000	CR		Ever	Ever
94	Pcb	F	5, 04	<50,000	SR	Under	<1000	Abn		Never	Never
95	Cip	M	3, 03	<50,000	SR	Well	<1000	CR		Never	Never
96	Pcb	F	2, 02	<50,000	SR	Well	<1000	CR		Never	Never
97	Pcb	M	1, 01	<50,000	HR	Well	<1000	CR		Never	Never

(*Continued*)

Table 6 (*Continued*)

Patient	Random	Sex	Age (years, months)	WBC count (/μl)	Risk group	Nutritional state	Day 8 response (/μl)	Induction outcome	Cause of death	Fever	Sepsis
98	Pcb	F	8, 02	≥50,000	HR	Under	<1000	CR		Never	Ever
99	Cip	F	6, 05	≥50,000	HR	Well	<1000	Abn		Never	Never
100	Cip	M	4, 09	≥50,000	HR	Well	<1000	Death	Intracranial hemorrhage	Never	Ever
101	Pcb	F	4, 00	≥50,000	HR	Under	<1000	CR		Never	Ever
102	Pcb	F	3, 06	<50,000	SR	Well	<1000	CR		Ever	Ever
103	Cip	M	3, 01	<50,000	HR	Under	≥1000	CR		Never	Never
104	Pcb	F	14, 00	<50,000	HR	Well	<1000	CR		Ever	Never
105	Cip	M	3, 11	<50,000	SR	Well	<1000	CR		Never	Ever
106	Pcb	M	8, 04	<50,000	HR	Well	≥1000	CR		Never	Never
107	Pcb	M	12, 01	<50,000	HR	Under	<1000	CR		Never	Never
108	Cip	M	3, 06	<50,000	SR	Under	<1000	CR		Ever	Never
109	Cip	F	5, 06	<50,000	SR	Well	<1000	CR		Never	Never
110	Cip	F	5, 03	<50,000	SR	Well	<1000	CR		Ever	Ever

Abbreviations: Cip, ciprofloxacin; Pcb, placebo; F, female; M, male; SR, standard risk; HR, high risk; Well, well-nourished; Under, undernourished; CR, complete remission; RD, resistant disease; Abn, abandonment to treatment.

case: the arm A tablets indeed contained ciprofloxacin, and those of arm B were placebo. The finding of more toxic death in the ciprofloxacin arm in our study was contrary to most previous studies, which have shown reduced events of fever, sepsis, or mortality.[6,9,27,28] We did not ascertain a definite cause for this finding.

Side effects related to ciprofloxacin in our study were mild and manageable, limited to nausea or vomiting and diarrhea as reported in previous studies.[29,30] Neutropenia or marrow suppression caused by ciprofloxacin is rare.[25] When we checked our database, however, we found that the ciprofloxacin group had a lower nadir of absolute neutrophil count. This may explain the higher incidence of fever, sepsis and death. It may moreover influence the gut flora or gut mucosa in a negative way, facilitating pathogens to invade into the circulation. We thought that the lower nadir of neutrophil count in the ciprofloxacin group may have been a predisposing factor to fever and infection, sepsis, and death in this study. It is reasonable to assume that patients who got sepsis were at greater risk of death.

Another jeopardizing impact of ciprofloxacin and fluoroquinolone is the emergence of resistant bacteria after its administration as prophylactic antibiotic,[31–36] but we could not find evidence for this because we were not able to conduct microbiological surveillance in this study. A further limitation was the bitter taste of ciprofloxacin, which might have influenced compliance to take the tablets when the patients were at home. High induction death rate in our study was related to the setting in Dr Sardjito Hospital, where childhood ALL patients were nursed in a general pediatric ward, and lack of supportive care. Occasionally, unavailability of medicines and late initiation of intravenous antibiotic therapy in neutropenic patients with fever also contributed to our high death rate. Due to lack of microbiological data, we could not show the cause of the infective deaths.

Conclusion

The use of ciprofloxacin prophylaxis after chemotherapy in childhood ALL is not warranted in our setting. Further study is needed to determine the rational use of ciprofloxacin in low-income countries and to limit the risk of the occurrence of microbial resistance to this important class of antibiotics.

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Disclosure

The authors report no conflicts of interest in this work.

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