Journal of Microbiology, Immunology and Infection 57 (2024) 879—886

Available online at www.sciencedirect.com

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Original Article

The clinical impact of primary granulocyte-colony stimulating factor prophylaxis in children with acute lymphoblastic leukemia who underwent induction chemotherapy

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Received 9 January 2024; received in revised form 11 June 2024; accepted 12 August 2024
Available online 20 August 2024

KEYWORDS
Acute lymphoblastic leukemia;
Breakthrough infections;
Children;
Granulocyte-colony stimulating factor;
Prophylaxis

Abstract *Background:* Data describing the risk factors for the occurrence of severe infections in acute lymphoblastic leukemia (ALL) patients following induction chemotherapy and the role of prophylactic granulocyte-colony stimulating factor (G-CSF) in the era of antimicrobials prophylaxis are limited.
Methods: This study enrolled 188 children aged ≤18 years with newly diagnosed ALL who received Taiwan Pediatric Oncology Group ALL-2002 and 2013 treatments between January 1, 2010 and June 30, 2021. Prophylactic G-CSF was administered when a patient continues neutropenia after achieving the first bone marrow remission since June 1, 2015. Clinical factors were assessed for their association with severe infections.
Results: From January 2010 to May 2015, 80 children experienced a total of 11 (13.5%) episodes of severe infections; while 10 (9.2%) episodes were reported to occur in 108 patients who received prophylactic G-CSF. Reduction of severe infections occurrence did not achieve statistical significance during prophylactic G-CSF administration in ALL patients. Compared with ALL-high risk (HR) and very high risk patients with no G-CSF prophylaxis, the use of G-CSF prophylaxis significantly reduced episodes of febrile neutropenia. Occurrence of grade III-IV

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https://doi.org/10.1016/j.jmii.2024.08.004

intestinal ileus, grade II-III oral mucositis, prolonged neutropenia, central venous catheter (CVC) placement, or the requirement insulin therapy for hyperglycemia were associated with higher risk of bloodstream infections.
Conclusions: ALL-HR patients with G-CSF prophylaxis were associated with reduction of febrile neutropenia episodes. Occurrence of severe ileus, oral mucositis, hyperglycemia, CVC placement, or prolonged neutropenia were associated with severe infections in ALL patients receiving induction chemotherapy.

Introduction

The survival rate of childhood Acute Lymphoblastic Leukemia (ALL) has significantly improved in recent decades, which has been attributed to various factors.[1] Among these factors, reducing the occurrence of life-threatening infections was a crucial element.[2] In pediatric ALL patients undergoing induction chemotherapy, the use of prophylactic antimicrobial agents during the afebrile neutropenic period significantly reduced the incidence and mortality associated with severe infections.[3] Nevertheless, there remained a 5—10% incidence of breakthrough severe infections in ALL patients despite the use of antimicrobial prophylaxis as previously reported.[3,4] Furthermore, 4% of pediatric ALL patients succumbed to infections during chemotherapy with the majority (48%) occurring during the induction phase, surpassing any other chemotherapy phase.[4,5] Therefore, evaluating the factors associated with severe infections during the induction chemotherapy and implementing interventions may further mitigate the risk of severe infection.

Based on previous reports, the use of prophylactic granulocyte-colony stimulating factor (G-CSF) during induction chemotherapy in adult ALL patients has been shown to shorten the neutropenic period, further reducing the incidence of severe infections, lowering disease relapse rates, and improving leukemia disease-free survival.[6] However, in previous pediatric ALL studies, the prophylactic use of G-CSF during induction chemotherapy did not decrease frequency of hospitalizations related to febrile neutropenia or improve treatment outcomes.[7] Given the enhanced intensity of current pediatric ALL induction chemotherapy in comparison to the past, employing multiple regimens of chemotherapy may lead to prolonged neutropenia and an increased rate of severe infections, particularly among high risk/very high risk (HR/VHR) ALL patients.[8] In the era of prophylactic antimicrobial use, there have been no studies reporting whether prophylactic G-CSF use can shorten the neutropenic period and further reduce the incidence of severe infections during induction chemotherapy.

To understand the impact of prophylactic G-CSF use on the occurrence of afebrile neutropenia and severe infections during induction chemotherapy in pediatric ALL, the study institution initiated a protocol: G-CSF prophylaxis in cases of severe neutropenia, starting from June 1, 2015. The primary objectives of this study are to evaluate the incidence of severe infections, the duration of neutropenia and the frequency of febrile neutropenia (FN) during induction chemotherapy in pediatric ALL when prophylactic G-CSF is used in the era of prophylactic antimicrobial agents between 2010 and 2021. The secondary objective is to investigate risk factors for severe bacterial and fungal infections during induction chemotherapy in pediatric ALL, providing potential strategies for preventing severe infections during induction chemotherapy in the future.

Methods

This study is a single-center longitudinal study conducted at Mackay Children's Hospital. Between January 1, 2010, and June 30, 2021, a total of 188 children aged $\leq$18 years with newly diagnosed ALL were enrolled. Children with ALL received sequential treatment protocols based on the timing of their diagnosis, including the Taiwan Pediatric Oncology Group (TPOG) -ALL-2002 and TPOG-ALL-2013 protocols. We recorded and compared the differences in patient characteristics, infection events, and episodes of FN between the pre G-CSF prophylaxis period (January 2010 to May 2015) and the G-CSF prophylaxis period (June 2015 to June 2021). We also analyzed the efficacy of G-CSF prophylactic treatment and potential factors contributing to breakthrough infections. This study was approved by the Mackay Hospital Institutional Review Board (23MMHIS332e, 24MMHIS169e), and all participants or their legal guardians provided written informed consent for ALL treatment following the Helsinki Declaration. The TPOG ALL-2002 induction chemotherapy was previously described in a report.[9] The induction chemotherapy of TPOG ALL-2013 was based on TPOG ALL-2002 with modifications (Supplementary table 1). ALL-2013 is a treatment protocol based on treatment response, minimal residual disease (MRD): children with provisional ALL-standard risk (SR) who, on the 15th day of induction chemotherapy (MRD I) have MRD $\geq$1%, or at the end of induction (MRD II) have MRD $\geq$0.01%, are reclassified as ALL-high risk (HR).

From January 1, 2010 to June 30, 2021, prophylactic antimicrobials were administered to ALL patients experiencing afebrile neutropenia during induction chemotherapy. Oral ciprofloxacin was given at a dose of 300 mg/m^2 every 12 hours, along with micafungin at a dose of 1 mg/kg/day, with a maximum dose of 50 mg. This prophylactic antimicrobials treatment was initiated once the patient's absolute neutrophil count (ANC) reached $\leq$500/μL and was expected to remain so for more than 7 days during induction chemotherapy. Starting from January 2013, vancomycin, at a dose of 400 mg/m^2/dose every 12 hours, was introduced at the onset of neutropenia. The prophylaxis

with antimicrobials was discontinued once the ANC recovered to ≥100/μL post-nadir.

Prophylactic G-CSF (CHUGAI Pharma Taiwan LTD., 100/300 mcg/vial) administration subcutaneously with a dosage of 200 mcg/m^2/day[10–12] was initiated when patients achieved their first bone marrow remission on day 16 of induction therapy and still had neutropenia (ANC≤ 300/μL) starting from June 1, 2015. The use of G-CSF was discontinued when the ANC began to recover to greater than 300/μL or when myeloid precursor cells appeared in peripheral blood. All infection events that occurred during the pre-G-CSF prophylaxis period (January 2010 to May 2015) and the G-CSF prophylaxis period (June 2015 to June 2021) were recorded, including bacterial and fungal infections in various locations such as blood, urine, gastrointestinal tract, and tissues (Supplementary table 2). The types of pathogens responsible for bloodstream infection (BSI), and the antimicrobial susceptibility were documented (Supplementary table 3).

In the analysis, infection events occurring after day 16 were considered separately between the two periods, as G-CSF prophylactic treatment commenced after this point. Various clinical factors related to breakthrough infections during induction chemotherapy were recorded and analyzed, including the ALL risk group, the use of prophylactic G-CSF, the duration of neutropenia exceeding 14 days, FN, the insertion of central venous catheter (CVC), hyperglycemia requiring insulin therapy, the presence of grade II-III oral mucositis, and grade III-IV intestinal ileus, to determine their relevance to infection occurrence (Table 5). At our institution, children with ALL do not routinely receive Port-A placement during induction chemotherapy for avoiding delay treatment and increase infection risk. Instead, they receive a non-tunneled CVC due to difficulties with peripheral intravenous injections. Children with ALL might experienced hyperglycemia during induction chemotherapy due to treatment with prednisolone and L-asparaginase. The criteria for initiating insulin therapy for hyperglycemia are as follows: 1. Finger stick glucose ≥200 mg/dL on two occasions within 12 hours, 2. Urine glucose measurable for consecutive two days, 3. HbA1c ≥ 6.5%.

Definitions

Infection events are defined as infections microbiologically confirmed. Skin infections include clinical diagnoses of abscesses, bacterial dermatitis, or furuncles, confirmed through culture. Urinary tract infections encompass infections involving any part of the urinary system, confirmed through urine culture. Gastrointestinal infections comprise diarrhea and infections confirmed through fecal culture. Breakthrough infections are defined as proven invasive bacterial or fungal infections occurring on or after the third day of prophylactic antimicrobial use. The National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0)[13] were utilized to define all infection events where ≥ grade 3 was recorded. Febrile Neutropenia (FN) is defined as a situation where the core body temperature is ≥ 38.3 °C or ≥ 38.0 °C and sustained for at least 1 h in the presence of neutropenia. At the study institution, the strategy for managing FN aligns with prior descriptions.[14] The definition of severe infections includes bloodstream bacterial infections and invasive fungal infections (IFI). Bloodstream Infection (BSI) is defined as the isolation of a known pathogen from ≥1 blood culture, unrelated to infections in other locations, and accompanied by clinical signs of systemic infection. If a common commensal organism (e.g., methicillin-resistant coagulase-negative staphylococci) is isolated from two blood cultures in patients with ANC ≤0.5 × 10^9/L, it is recorded as the true pathogen for BSI.[15] Invasive Fungal Infection (IFI) is defined as fungemia and/or visceral dissemination of fungi.[16]

Statistical analysis

Comparisons between the groups, including the development of bacterial and fungal infections, episodes of FN, and clinical features for children with ALL receiving ALL-2013 protocol, were estimated using the independent sample t-test and chi-square test. Since ALL patients may receive antimicrobial treatment at the time of diagnosis or during the neutropenic period due to bacterial or fungal infections, which could further affect the occurrence of infections and the use of antimicrobials after day 16, a binary regression model was employed to assess the risks of any breakthrough infections, episodes of FN, and factors associated with BSI development for all children with ALL during induction chemotherapy. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc., IBM Corp., Armonk, NY, USA). A significant level of $P < 0.05$ was applied.

Results

A total of 188 patients with newly diagnosed pediatric ALL were enrolled for study between January 1, 2010 and June 30, 2021. Based on whether they received G-CSF prophylactic treatment, patients receiving ALL-2013 chemotherapy were divided into two groups: 51 patients did not receive G-CSF prophylaxis (pre G-CSF prophylaxis period: January 2013 to May 2015) while 108 patients received G-CSF prophylaxis (G-CSF prophylaxis period: June 2015 to June 2021). There were no significant differences in patient characteristics between the two groups, regardless of age, gender, ALL immunophenotype, and ALL risk classifications (Table 1). For both the pre-prophylactic and prophylactic treatment periods, there were no statistically significant differences in the occurrence of BSI or IFI (Table 2). Among the patients treated under the ALL-2013 protocol, 17 provisional ALL-SR patients were reclassified as ALL-HR during induction chemotherapy, including 10 patients at MRD I and 7 patients at MRD II. One 4 year-old girl, diagnosed with ALL-HR, developed *Escherichia coli* sepsis on day 15 of induction chemotherapy without G-CSF prophylaxis and subsequently died. Most patients receiving G-CSF injections were tolerable without severe adverse effects and only a small number of patients experienced low back pain (4/108, 4%), and fever (6/108, 6%).

There were also no significant differences between the two groups in duration of neutropenia, length of hospital stay (Table 3). However, the use of G-CSF prophylactic

Table 1 Patient characteristics by use of G-CSF and without G-CSF included in the study from 2013 to 2021.

Characteristics	Total (n = 159, %)	Without G-CSF prophylaxis (n = 51, %)	With G-CSF prophylaxis (n = 108, %)	*p*
Gender				
Male	88 (55.3)	25 (49.0)	63 (58.3)	0.270
Female	71 (44.7)	26 (51.0)	45 (41.7)	
Age, yr				
Median age (range)	4.5 (0.2—17.9)	4.4 (0.4—17.2)	4.5 (0.2—17.8)	0.485
≥10	35 (22.0)	14 (27.4)	21 (19.4)	0.290
1-10	116 (73.0)	36 (70.5)	80 (74.1)	
<1	8 (5.0)	1 (1.1)	7 (6.4)	
Subtype				
B-ALL	145 (91.2)	48 (94.1)	97 (89.8)	0.371
T-ALL	14 (8.8)	3 (5.8)	11 (10.2)	
WBC counts (10^3/uL)				
Median WBC (range)	7.4 (1.2—575)	14.7 (2.4—560)	6.6 (1.2—575)	0.348
>100	38 (23.9)	17 (33.3)	21 (19.4)	0.055
<100	121 (76.1)	34 (66.7)	87 (80.6)	
ALL Risk				
SR	70 (44.0)	20 (39.2)	50 (46.3)	0.401
HR/VHR	89 (56.0)	31 (60.8)	58 (53.7)	
Induction days				
Median days (range)	36 (19—115)	36 (33—115)	36 (19—91)	0.307
In SR	35 (33—41)	35 (33—41)	35 (34—39)	0.857
In HR/VHR	40 (19—115)	39 (34—115)	40 (19—91)	0.415

Abbreviations: Acute lymphoblastic leukemia (ALL), Granulocyte colony-stimulating factor (G-CSF), High risk (HR), Standard risk (SR), Very high risk (VHR), White blood cell count (WBC), Years-old (yr).

Table 2 Comparison of patients with bacterial, fungal infection included in the study from 2013 to 2021.

	Total (n = 159)	Without G-CSF prophylaxis (n = 51, %)	With G-CSF prophylaxis (n = 108, %)	*p*
Bacterial BSI				
Total BSI	16 (10.0)	7 (13.7)	9 (8.3)	0.173
Gram positive	4 (2.5)	3 (5.9)	1 (0.9)	
Gram negative	12 (7.5)	4 (7.8)	8 (7.4)	
No BSI	143 (90.0)	44 (86.3)	99 (91.7)	
BSI between day 15 - EOI	12 (7.5)	6 (11.7)	6 (5.6)	0.166
Invasive fungal infections	3 (1.9)	2 (3.9)	1 (0.9)	0.195

Abbreviations: Bloodstream infection (BSI), End of induction (EOI), Granulocyte colony-stimulating factor (G-CSF).

treatment after day 16 of induction chemotherapy significantly reduced the occurrence of episodes of FN and the duration of neutropenia, especially for children with HR/VHR ALL compared to patients without prophylactic treatment (Table 3).

The relationship between the occurrence of breakthrough infections in pediatric HR/VHR ALL patients during induction chemotherapy through 2010 to 2021 and prophylactic G-CSF therapy was further assessed. We found that patients not receiving prophylactic G-CSF therapy had a 3.6 times higher risk of developing any breakthrough bacterial infections compared to those receiving prophylactic therapy, a result that reached statistical significance (Table 4). Patients not receiving prophylactic G-CSF therapy, had a 2.6 times higher risk of developing breakthrough BSI and a 1.8 times higher risk of FN, but these differences did not reach statistical significance (Table 4). In the analysis, infection events occurring after day 16 were considered separately between the two periods, as G-CSF prophylactic treatment commenced after this point. Risk assessment for the occurrence of BSI in pediatric ALL during induction chemotherapy through 2010 to 2021 was also conducted. We observed that during induction chemotherapy, if patients experienced grade III-IV intestinal ileus, grade II-III oral mucositis, neutropenia lasting more than two weeks, CVC placement, or required insulin therapy for hyperglycemia, the risk of BSI occurrence had ORs of 12.6, 5.6, 6.3, 5.9, and 7.0, respectively. All of these findings reached statistical significance (Table 5). In the current study, 12 patients received the placement of a non-

Table 3 Comparison of episodes of febrile neutropenia, duration of neutropenia, length of hospital stay during ALL-2013 induction chemotherapy.

Variables	Total			Standard Risk			High risk/Very High Risk		
	Without G-CSF prophylaxis (n = 51)	With G-CSF prophylaxis (n = 108)	*p*	Without G-CSF prophylaxis (n = 20)	With G-CSF prophylaxis (n = 50)	*p*	Without G-CSF prophylaxis (n = 31)	With G-CSF prophylaxis (n = 58)	*p*
Episodes of FN (%)									
At diagnosis	5 (9.8)	16 (14.8)	0.383	3 (15.0)	9 (18.0)	0.763	2 (6.4)	7 (12)	0.402
Day 1 - day 15	1 (2.0)	9 (8.3)	0.128	1 (5.0)	4 (8.0)	0.659	0 (0)	5 (8.6)	0.092
Day 16 - EOI	19 (37.3)	22 (20.4)	0.023	6 (30.0)	7 (14.0)	0.119	13 (41.9)	15 (25.9)	0.119
Duration of neutropenia, median days (range)	17 (2—56)	14 (0—43)	0.029	15 (3—33)	13 (0—28)	0.254	19 (2—56)	14 (0—43)	0.07
Day 1- day 15	6 (0—14)	7 (0—14)	0.885	10.5 (0—14)	8 (0—14)	0.474	3 (0—14)	5 (0—14)	0.512
Day 16 - EOI	9 (0—50)	5 (0—16)	<0.001	4.5 (0—19)	4 (0—16)	0.261	11 (0—50)	5 (0—16)	<0.001
G-CSF use, median days (range)	3 (0—35)	6 (0—32)	0.270	5 (0—15)	5 (0—17)	0.613	3 (0—35)	8 (0—32)	0.163
Length of hospital stay median days (range)	31 (22—94)	30 (13—95)	0.686	29 (22—37)	26 (22—41)	0.288	39 (22—94)	43 (13—95)	0.862

Abbreviations: End of induction (EOI), Febrile neutropenia (FN), Granulocyte colony-stimulating factor (G-CSF).

Table 4 Relationship between prophylactic G-CSF use and occurrence of breakthrough infections in pediatric HR/VHR ALL during induction chemotherapy from 2010 to 2021.

Without prophylactic G-CSF administration			
	OR	95% CI	*p*
Breakthrough BSI	2.611	0.84—8.118	0.097
Breakthrough any bacterial infections	3.635	1.226—10.784	0.02
Breakthrough IFI	2.752	0.245—30.932	0.412
Breakthrough any fungal infections	0.759	0.213—2.703	0.671
Episode of FN	1.8	0.945—3.43	0.074

Abbreviations: Acute lymphoblastic leukemia (ALL), Bloodstream infection (BSI), Confidence interval (CI), Febrile neutropenia (FN), Granulocyte colony-stimulating factor (G-CSF), High risk (HR), Invasive fungal infection (IFI), Odds ratio (OR), Very high risk (VHR).

Table 5 Risk factors of bacterial bloodstream infections in pediatric ALL during induction chemotherapy from 2010 to 2021.

	OR	95% CI	*p*
Grade III-IV Ileus	12.617	2.758—57.720	0.001
Grade II-III Oral mucositis	5.630	1.226—25.853	0.026
Duration of neutropenia ≥2 weeks	6.390	1.612—25.323	0.008
CVC placement	5.907	1.390—25.111	0.016
Hyperglycemia with insulin therapy	7.083	1.007—49.832	0.049
Without G-CSF administration	0.897	0.246—3.275	0.869
Without TPN administration	0.234	0.021—2.604	0.237

Abbreviations: Acute lymphoblastic leukemia (ALL), Central venous catheter (CVC), Confidence interval (CI), Granulocyte colony-stimulating factor (G-CSF), Odds ratio (OR), Total parenteral nutrition (TPN).

tunneled CVC during induction chemotherapy and 7 patients experienced hyperglycemia necessitating subsequent insulin therapy.

Discussion

This report presents an analysis of the clinical results of children with ALL who received prophylactic G-CSF during induction chemotherapy while experiencing afebrile neutropenia. It is also the first report conducted in a setting where patients simultaneously received antimicrobials prophylaxis. This study had several findings. Firstly, the use of prophylactic G-CSF significantly reduced the incidence of FN episodes and shortened the duration of neutropenia after the 15th day of induction chemotherapy in HR/VHR ALL patients. Secondly, HR/VHR ALL patients who did not receive prophylactic G-CSF therapy were at a higher risk of developing breakthrough bacterial infections compared to those who received prophylactic treatment. Lastly, the occurrence of grade III-IV intestinal ileus, grade II-III oral mucositis, prolonged neutropenia exceeding two weeks, CVC placement, and the need for insulin therapy due to hyperglycemia were identified as factors associated with BSI in children with ALL undergoing induction chemotherapy. These results suggest that the use of prophylactic G-CSF in HR/VHR ALL patients during induction chemotherapy may be a reasonable practice.

Recent reports indicate that the use of antimicrobials prophylaxis during afebrile neutropenia in newly diagnosed pediatric ALL patients undergoing induction chemotherapy can effectively reduce the incidence of BSI and FN.[3,4,8,14] The fluoroquinolones class of drugs has the most supporting evidence among those antibiotics prophylaxis studies in ALL.[17] Ciprofloxacin was the first drug

reported for use, but due to its lower sensitivity in treating *Streptococcus* spp., particularly viridans group streptococci, it has been largely replaced by levofloxacin in clinical practice recently.[17]

In pediatric cancer patients, three main factors contribute to the occurrence of IFI: first, the breakdown in natural barriers, such as catheter placement and mucositis; second, cellular immune deficits resulting from lymphocyte depletion due to corticosteroids and other T-cell cytotoxic drugs; and third, insufficient phagocytic cell counts due to myelosuppressive chemotherapy.[18] A single defect in a patient's defense system is often insufficient to lead to opportunistic IFI, but with multiple deficiencies coexisting, the likelihood of IFIs significantly increases.[19] There have been reports confirming that the prophylactic antifungal therapy during afebrile neutropenia lasting seven days in children with newly diagnosed ALL undergoing induction chemotherapy can effectively reduce the occurrence of IFIs.[14] Voriconazole was among the first prophylactic antifungal agents reported.[20,21] However, due to the severe neurotoxicity resulting from the concurrent use of voriconazole with vincristine, one common chemotherapeutic agent used during induction chemotherapy for pediatric ALL,[22] recent studies have shifted to using echinocandin-class drugs to replace voriconazole.[19] Micafungin is the most commonly used among echinocandin-class antifungals, demonstrating a sensitivity to *Aspergillus* or *Candidas* similar to caspofungin[19,20], while being significantly more cost-effective. In the current study, the cases of fungal infections in the gastrointestinal tract were higher in the G-CSF group, possibly due to recent changes in our strategy for managing severe diarrhea in patients with cancer undergoing chemotherapy, as shown in Supplementary Table 2. This phenomenon may be explained by the fact that, at our institution, patients with cancer experiencing severe diarrhea during chemotherapy were previously treated primarily with antidiarrheal medications. However, we now conduct multiple tests, including stool bacterial and fungal cultures, rotavirus antigen testing, and Clostridium toxin and antigen testing. Stool pathogen examination may be a significant factor contributing to the higher rate of fungus isolated from stool samples.

In one multicenter randomized trial, it was indicated that the use of levofloxacin prophylaxis significantly reduced the incidence of BSI; however, 9.3% of patients still experienced breakthrough BSI caused by viridans group streptococci and Gram-negative bacteria.[3] Possible reasons for the breakthrough BSI may include differences in the bacterial spectrum of activity, inter-individual variations in oral drug absorption, or issues related to medication compliance.[3]

In children with cancer who underwent antifungal prophylaxis, whether using caspofungin or posaconazole, approximately 10% of patients still experienced breakthrough IFIs during chemotherapy.[23,24] Possible causes of breakthrough fungal infections include point mutations in the FKS1 gene leading to reduced echinocandin susceptibility when using caspofungin,[23] and the co-administration of proton pump inhibitors with posaconazole affecting drug blood levels.[24] The main distinction between the current report and previous literature is the simultaneous administration of G-CSF prophylaxis to patients under antimicrobial prophylaxis. G-CSF prophylaxis may be associated with a lower rate of breakthrough infections, as demonstrated by 5% of breakthrough BSI and 0.6% of breakthrough IFI in the current report, compared to previous reports. We also observed that the pathogens responsible for 75% (6 out of 8) breakthrough BSI cases in this study were ciprofloxacin-resistant bacteria. Although the antibiotic susceptibility of the most common bacterial organisms did not change before or after the implementation of antibiotics prophylaxis strategies based on a study institution survey,[3] the lack of change in antibiotics susceptibility may be due to the relatively low proportion of pediatric ALL cases within the entire study institution. The significant proportion of ciprofloxacin-resistant breakthrough BSI raises the question of whether prophylaxis strategies should be limited to high-risk ALL patients or whether the addition of G-CSF prophylaxis to reduce the duration of antibiotics prophylaxis should be considered.

Reviewing the literature, the use of G-CSF during chemotherapy has been shown to shorten the duration of neutropenia and improve the severity of neutropenia,[9] reduce length of hospital stay,[25] decrease the occurrence of FN,[26] lower the readmission rate due to FN,[27] and even correlate with improved long-term outcomes in T-ALL and young adult patients.[26] However, current guidelines from NCCN[28] and ASCO[29] only recommend the use of primary G-CSF prophylaxis to prevent severe infections when patients experience FN during chemotherapy.[30] Thus, the practice of using primary G-CSF prophylaxis in pediatric ALL patients during afebrile neutropenia in induction chemotherapy remains controversial. Therefore, further assessment of the clinical outcomes of pediatric ALL patients undergoing antimicrobials prophylaxis while using prophylactic G-CSF is necessary. Based on our study, the primary G-CSF prophylaxis strategy should be recommended only for HR/VHR ALL patients during afebrile neutropenia or in cases involving pediatric ALL patients with severe neutropenia (ANC$<$100/μL), life-threatening conditions, and febrile neutropenia.

In a retrospective study involving a large population of children with ALL undergoing chemotherapy, it was observed that patients were most prone to infections during the induction chemotherapy. Notably, FN was the most prevalent infection-related complication during induction chemotherapy.[8] HR ALL patients had a higher risk of experiencing FN and various infections compared to low-risk ALL patients, primarily because of the higher chemotherapy doses administered early in their treatment.[8] In the current study, we further identified risk factors for BSI in pediatric ALL patients receiving induction chemotherapy. These risk factors included severe intestinal ileus and oral mucositis, neutropenia lasting more than two weeks, CVC placement, and the required insulin therapy for hyperglycemia. The occurrence of severe intestinal ileus or hyperglycemia is often attributed to the use of chemotherapeutic agents such as vincristine and asparaginase.[9,31] On the other hand, oral mucositis and prolonged neutropenia can be improved through the administration of G-CSF. These findings underscore the multiple clinical factors associated with the occurrence of severe infections in ALL patients during the induction chemotherapy, and they rationalize that G-CSF prophylaxis therapy alone cannot completely prevent the onset of BSI.

Therefore, to reduce the incidence of breakthrough infections in ALL patients during induction chemotherapy, a comprehensive approach involving multiple strategies may be necessary in supportive care. For example, enhancing oral hygiene to decrease the severity of oral mucositis or placing CVCs only when absolutely necessary.

Our study has several limitations. First, it is a historical comparative study rather than a randomized controlled trial and spans a relatively long study period of 12 years. Therefore, the occurrence of breakthrough infections may be influenced by various factors, which in turn may affect the clinical results of prophylactic G-CSF. Second, this is a single-center study with a relatively small number of cases, which limits our ability to further analyze other factors, including the impact of changes in primary pediatric cancer clinical staff, modifications to the ward environment (The pediatric oncology ward was renovated in 2014), and differences in patient populations involving a higher proportion of children with foreign parents. All of these factors could potentially impact the occurrence of infections during treatment.

In conclusion, in the context of pediatric ALL patients undergoing induction chemotherapy with antimicrobials prophylaxis, the concurrent use of primary G-CSF prophylaxis in afebrile neutropenia yields the following clinical findings: first, in HR/VHR ALL patients, it significantly reduces the incidence of FN and the duration of neutropenia after induction chemotherapy day 15; second, it lowers the rate of any bacterial infections in HR/VHR ALL patients; finally, we have also demonstrated that several clinical conditions are associated with the occurrence of BSI in ALL patients during induction chemotherapy, including grade III-IV intestinal ileus, grade II-III oral mucositis, neutropenia lasting more than two weeks, CVC placement, and the requirement insulin therapy for hyperglycemia.

CRediT authorship contribution statement

Yi-An Lu: Conceptualization, Data curation, Writing — original draft. **Hsi-Che Liu:** Investigation, Methodology, Project administration. **Jen-Yin Hou:** Data curation, Investigation, Methodology. **Nan-Chang Chiu:** Conceptualization, Resources. **Ting-Huan Huang:** Conceptualization, Project administration. **Ting-Chi Yeh:** Conceptualization, Formal analysis, Writing — review & editing.

Declaration of competing interest

None.

Acknowledgments

I would like to express my gratitude to all of the Mackay Memorial Hospital mentors who have inspired and guided me through the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.08.004.