Epidemiology of Invasive Fungal Disease in Pediatric B-Cell Acute Lymphoblastic Leukemia

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Background

- Children with B-cell acute lymphoblastic leukemia (B-ALL) have increased risk of infections
- Invasive fungal disease (IFD) is an important cause of morbidity and mortality in B-ALL patients
- Data regarding the epidemiology of IFD in pediatric B-ALL patients is needed to inform prophylaxis strategies and empirical treatment decisions

Objective:
Describe the epidemiology of IFD in children and young adults with de novo B-ALL treated at Cincinnati Children's Hospital Medical Center (CCHMC)

Methods

Retrospective cohort study of children with B-ALL treated at CCHMC from 01/2011-12/2022

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Chart review, abstracting data related to chemotherapy course, antifungal prophylaxis, microbiology data, and outcomes

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Identification of IFD episodes using:
•Culture data
•Histopathology
•Imaging
•Biomarkers

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Calculated overall and course-specific incidence

Results

- Cohort included 250 children treated for B-ALL at CCHMC
- A total of 9/250 (3.2%) developed IFD during B-ALL treatment at CCHMC
- There were no differences in age, sex, or overall outcomes between those with and without IFD (Table 1)

Table 1: Clinical characteristics of the patient cohort

Characteristic	Developed IFD (n=9)	Did not develop IFD (n=241)	p-value
Age at diagnosis, median (IQR)	**9.14 (1.01-15.36)**	**5.00 (3.18-11.72)**	**0.82**
Female sex, n (%)	**2 (22.2%)**	**109 (48.9%)**	**0.12**
Trisomy 21, n (%)	**0 (0%)**	**10 (4.1%)**	**0.53**
Development of relapsed ALL, n (%)	**1 (11.1%)**	**33 (13.7%)**	**0.82**
Death, n (%)	**1 (11.1%)**	**12 (5.0%)**	**0.42**

Epidemiology
- Four proven mold infections occurred during induction (n=3) and consolidation (n=1)
- There were two infections involving yeasts that occurred during a blinotumomab block and the IB course of Interfant-06
- Two cases of proven *Pneumocystis jiroveci* pneumonia (PJP) and one case of probable PJP occurred during maintenance or continuation therapy
- There were no IFD cases in interim maintenance or delayed intensification
- Incidence-rates are shown in Table 2

Clinical Outcomes
- Of children with IFD, 5/9 (55.6%) were on antifungal prophylaxis at the onset of infection
- The infecting organism was resistant to prophylaxis in 4/9 (44.4%) cases
- All patients received treatment directed at their infection
- Only 1/12 (8.3%) died from their IFD

Table 2: Incidence of IFD during treatment of B-ALL

Course	# IFD events	Total Days	IFD/1000 patient-days	IFD per patient-month
Induction	3	8113	0.370	0.011
Consolidation	1	9301	0.108	0.003
Interim Maintenance	0	21453	0.000	0
Delayed Intensification	0	14178	0.000	0
Maintenance	2	118098	0.017	0.001
Continuation	1	3512	0.285	0.009
Blinatumomab blocks	1	572	1.750	0.052

Conclusions

- Invasive fungal disease was uncommon in this single-center cohort of pediatric B-ALL patients
- Highest incidence in patients receiving intensive chemotherapy courses such as induction or consolidation
- *Pneumocystis jiroveci* pneumonia occurred during less intensive chemotherapy courses as well
- Mold-active prophylaxis should be administered during intensive courses
- *Pneumocystis jiroveci* pneumonia prophylaxis should be given throughout therapy

Future Directions

- Including T-cell acute lymphoblastic leukemia patients in the study population to capture additional IFD episodes
- Collection and evaluation of pharmaceutical prescribing information of antifungal prophylaxis both inpatient and outpatient
- Application of similar methods to pediatric acute myeloblastic leukemia patients, who may have differential incidence of IFD given more intensive chemotherapy

References

1.Donnelly, J.P., et al., *Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium.* Clin Infect Dis, 2020. **71**(6): p. 1367-1376.