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Risk Factors for Invasive Fungal Disease in Pediatric Oncology

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Abstract

Background: Invasive fungal infections are a major cause of death in pediatric oncology, especially among patients under chemotherapy. This study aims to identify risk factors for invasive fungal infections in pediatric oncology.

Methods: We conducted a monocentric retrospective case-control multi-cohort study on a population of 30 patients with malignant hemopathies or solid cancers under chemotherapy, admitted in the Pediatric Oncology unit of Nafissa Hammoud Hospital in Algiers, amongst which 24 patients were controls, and six patients were cases.

Results: In a total of 30 patients (53.3 % male), 13 patients developed a fever, from which six patients were identified as invasive fungal infection cases according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and Infectious Diseases Mycoses Study Group (EORTC/MSG) guidelines, with an incidence of 20%. The mean age was 7.47 years old at the admission date. Four statistically significant risk factors were identified (p-value < 0.05, CI 95 %): mucositis with an odds ratio (OR) at 10 (1,34 – 74,51), the most aggressive chemotherapy protocol according to the ITR2 with an OR at 115 (6,10 – 2165,95), severe prolonged neutropenia with an OR at 7,6 (1,07 – 54,09) and severe prolonged lymphopenia with an OR at 25 (2,27 – 275,71).

Conclusion: Many conditions were identified as risk factors for invasive fungal infections in pediatric oncology, especially severe lymphopenia and aggressive chemotherapy. These patients may have to receive close monitoring or even antifungal prophylaxis.

Keywords: invasive fungal disease, risk factors, pediatric oncology, mucositis, severe lymphopenia, chemotherapy intensity, acute myeloid leukemia

Introduction

Invasive fungal diseases (IFDs) are a major cause of morbidity and mortality in children [1] and especially with hematologic malignancies [2,3]. Thus, it is important to assess the clinical profile of patients with IFD, to initiate closer monitoring, or antifungal prophylaxis in higher-risk patients which has shown its efficiency in lowering mortality [4].

Many retrospective studies have been done in multiple centers in Europe and the United States of America, to determine the clinical picture, the risk factors, and the evolution of the disease, of inpatients in Pediatric Oncology units [3,5,6], however, data is still limited, and most of the studies were made in adult patients.

In 2016, Fisher and al. have made a systematic review to determine the risk factors of IFD in pediatric oncology and children undergoing hematopoietic stem-cell transplantation. They have shown that the most important risk factor was the presence of long-term febrile neutropenia [7]. Factors included in our study were based on the results reported in this paper.

The European Organization for Research and Treatment of Cancer/Mycology Study Group (EORTC/MSG) published an international consensus in 2002, revised in 2008 and 2021, to define, diagnose and treat IFD in immunocompromised patients with cancer or undergoing hematopoietic stem-cell transplant [8–10]. However, it is often hard to apply these recommendations in everyday practice, because of the systematic antifungal prophylaxis in our unit, the polymorphism of the clinical picture, and the difficulty to access the mycologic diagnosis methods in some centers.

This study is the first of its kind in Algeria, which aims to identify the incidence and risk factors of IFD in a pediatric oncology unit, following the EORTC/MSG diagnostic criteria.

Methods

This study is a case-control multi-cohort retrospective monocentric study, including patients hospitalized from March 1st, 2021 to September 31st, 2021 in the Pediatric Oncology Unit, and in the Pediatrics Department of Pr. Z. Zeroual, in Nafissa Hammoud Hospital in Algiers, with hematologic malignancies or solid cancers undergoing chemotherapy.

Cases of IFD have been identified during the study period, and divided into proven, probable, and possible, according to the revised and updated EORTC/MSG criteria [8–10]. IFDs are proven if there is direct evidence of infection by fungi in a sterile material, either by microscopic analysis or culture. IFDs are probable if there are host factors associated with both clinical and mycological factors.

37 patients were eligible for inclusion, two patients with retinoblastoma were excluded because they didn't meet our criteria, and five other patients were excluded due to lack of data.

Demographic data included age at admission, sex, and comorbidities. Clinical data included the presence of IFD according to the EORTC/MSG criteria, the underlying hematologic malignancy or solid cancer, the chemotherapy protocol, and its intensity classified according to the Intensity of Treatment Rating (ITR) scale 2.011, the presence of fever, mucositis, and central venous catheter (CVC). Biological data included the presence of long-term (> 10 days) severe neutropenia (< 500 elements/mm3) and long term (> 10 days) severe lymphopenia (< 100 elements/mm3). Therapeutic data included long-term (> 7 days) antibiotic intake and long-term (> 21 days) corticosteroid intake.

Data analysis was conducted using the Statistical Package for Social Science 26.0 (SPSS 26.0) software. Qualitative variables were evaluated with a Chi-square test. The statistical correlation was estimated by calculation of the odds-ration, with a p-value of 0.05 and a confidence interval of 95%.

Results

Descriptive statistics

Over seven months, 30 children (53,3% male) were included in the study, with a mean age of 7,47 years old at admission, with a minimum of one year old, and a maximum of 16 years old. The most frequent underlying malignancy in our population was acute lymphoblastic leukemia (ALL) with nine patients (30%), followed by non-Hodgkin lymphomas, most of which were Burkitt lymphomas, with seven patients (23.3%), then acute myeloid leukemia (AML) with six patients (20%), Hodgkin lymphomas with four patients (13,3%) and nephroblastomas and neuroblastomas with four patients (13,3%), three and one respectively.

Among all included patients, eight of them (26,7%) were under a moderately aggressive protocol according to the ITR-2. 17 of them (56,7%) were under a very aggressive protocol. Finally, five of them (16,7%) were under a most aggressive protocol. The patient's characteristics are shown in Table 1.

Incidence of IFDs

Over the study duration, 13 patients (43,3%) had an episode of fever, 6 of which (46,15%) were diagnosed with IFD. The overall incidence of IFDs in the unit is 20%, one (3,33%) is proven, one (3,33%) is probable and four (13,33%) are possible. The mortality rate of IFD patients is 33,33%.

Among the six cases of IFD, one was under a very aggressive protocol according to the ITR-2, and the remaining five were under a most aggressive protocol, and were all AMLs, except one relapse protocol for Burkitt lymphoma.

The most frequent localization of the disease was pulmonary in four patients (66,66%). There was one case of *Candida parapsilosis* sepsis and one cases of possible digestive candidosis with negative blood and stool culture.

We then compared the incidence of multiple risk factors for IFDs between cases and controls: the presence of mucositis, CVC, the most aggressive protocol according to ITR-2, long-term antibiotic or corticosteroid intake, and severe neutropenia or lymphopenia. The results are shown in Table 2.

Table 1: Characteristics of patients included in the study. Abbreviations: No: Sample number.

Characteristic	No.	Percentage (%)
Gender		
Male	16	53,3
Female	14	46,7
Age		
< 6 years old	9	30
6 to 12 years old	12	40
> 12 years old	9	30
Underlying disease		
Acute lymphoid leukemia	9	30
Acute myeloid leukemia	6	20
Non-Hodgkin lymphoma	7	23,3
Hodgkin Lymphoma	4	13,3
Neuroblastoma	1	3,3
Nephroblastoma	3	10
Protocol intensity		
Moderately intensive	8	26,7
Very intensive	17	56,7
Most intensive	5	16,7
Risk factors		
Mucositis	8	26,7
Central venous catheter	6	20
Antibiotic intake	14	46,7
Corticosteroid intake	11	36,7
Severe neutropenia	09	30
Severe lymphopenia	09	30

Risk factors for IFDs

The statistical correlation between these factors and the risk to develop IFD in our population was analyzed. The presence of mucositis, the most aggressive chemotherapy protocol, severe neutropenia, and lymphopenia were identified as potential risk factors and may increase the risk to develop an IFD among our population. Other

Table 2: Incidence of risk factors in cases and controls. Abbreviations: N: sample size

Factor	Cases (N=6)	Controls (N=24)
Mucositis	4 (66,67)	4 (16,67)
Central venous catheter	2 (33,33)	4 (16,67)
Most intensive protocol	5 (83,33)	1 (4,17)
Antibiotic intake	5 (83,33)	9 (37,5)
Corticosteroid intake	2 (33,33)	9 (37,5)
Severe neutropenia	5 (83,33)	4 (16,67)
Severe lymphopenia	5 (83,33)	4 (16,67)

factors don't seem to be statistically significant.

The most aggressive protocol according to ITR-2 (and especially ELAM-2 protocol for AML) and severe lymphopenia, seem to be the highest significant factors that increase the risk of IFD, with an odds ratio of 115 (6,10 - 2165,95) and 25 (2,27 - 275,71) respectively. The results are shown in Table 3.

Table 3: Odds-ratios of risk factors included in the study. Abbreviations: OR: Odds Ratios, CI: Confidence Interval.

Factor	p-value	OR (CI 95%)
Mucositis	0,013	10 (1,34 – 74,51)
Central venous catheter	0.361	2.5 (0,34 – 18.63)
Antibiotic intake	0.044	8.3 (0,84 – 83.17)
Corticosteroid intake	0.85	0.8 (0,12 – 5.5)
Most aggressive protocol	< 0,001	115 (6,10 – 2165,95)
Severe neutropenia	0,028	7,6 (1,07 – 54,09)
Severe lymphopenia	0,001	25 (2,27 – 275,71)

Discussion

The overall incidence of proven, probable, and possible IFDs in our study is 20%. It's more than the incidence found in literature, estimated between 4,9% and 7,2% [3,12,13]. This difference is due to the type of IFDs included: in literature studies, only proven and probable IFDs are accounted for in the calculation. The incidence of proven and probable IFDs in our study is 6,6%, which tallies the literature results.

It is difficult to compare incidence rates between different papers, due to different inclusion and exclusion criteria, the lack of diagnostic means to prove IFDs, and the systematic antifungal prophylaxis in our unit.

The mortality rate in patients with IFDs varies from 27,4% to 48%3, [13-15] according to the literature review. Our study has found a 33,33% mortality, which ties in literature results. This mortality rate includes death that is related to or independent of infection.

Among all risk factors in our study, long-term severe neutropenia was found in 83,33% of our patients, with an OR of 7,6 (p=0,028). In a previous paper written by Rosen et al., the incidence of severe neutropenia was 62%3. It was higher (77%) in Castagnola et al. study [14], and even higher according to Mor et al. with 89,3% [13]. The result of our study corresponds to the literature review.

Moreover, our results are similar to the literature concerning the impact of most intense chemotherapy, with an OR of 115 ($p < 0.001$), and the presence of mucositis with an OR of 10 (p=0,013) as risk factors for developing an IFD [13,16]. Mucositis may represent a starting point for invasive *Candida* infections [17]. The most aggressive protocols, especially those containing cytarabine, which is a well-known risk factor for invasive fungal infections [18].

Our study does not concur with the literature, especially Fiser et al. [7] findings, concerning long-term antibiotic and corticosteroid intake which do not seem to be statistically significant risk factors. This can be explained by the systematic antibiotic prophylaxis given to all our patients in our unit, and the low incidence of IFD in patients undergoing chemotherapy containing corticosteroids.

Finally, our paper identified long-term severe lymphopenia as a statistically significant risk factor with an OR of 25 ($p = 0,001$), which

corresponds to the results of Castagnola et al. [14] The risk is probably related to the implication of CD4+ lymphocytes in antifungal immune response [19]. There are little data about this particular topic, and more research should be done to confirm our results.

Limitations

This study has got limitations. It's a retrospective, monocentric study, made on a limited amount of patients, the results cannot be easily generalized to other centers. The duration of the study is short, and the number of IFD cases is hence small. We also regret the lack of diagnostic means, which restricts our possibility to prove fungal infections in our patients.

Conclusion

Despite these limitations, this study is the first step to future research on risk factors of IFD in pediatric oncology units. This research should be made on higher samples, and for a longer duration, to include more IFD cases.

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