INVASIVE FUNGAL INFECTIONS. RISK FACTORS AND EVOLUTION IN PATIENTS WITH MALIGNANT HEMOPATHIES

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Cuvinte cheie: *infecţii fungice invazive, hemopatii maligne, chimioterapie intensivă, neutropenie*

Abstract: *Invasive fungal infections are infectious complications with an increasing incidence, raising countless problems regarding the diagnosis and the treatment in children with malignant diseases. Objective. The analysis of invasive fungal infections in children with malignant hemopathies. Material and method. We underwent a retrospective analysis of invasive fungal infections on a lot of 132 patients with malignant hemopathies, treated in the Pediatric Clinic no 2 of Cluj-Napoca in the period 2001-2010. Results. The incidence of the invasive fungal infections was 9.8% of the total number of infectious episodes. We noted correlations between invasive fungal infections, prolonged severe neutropenia (p 0.000) and, respectively, antibiotherapy (0.000). Episodes were diagnosed as "possible" (60.7%), "probable" (21.4%) and "proven" (17.9%). Most frequent etiologies were Aspergillus and Candida spp. Mortality due to invasive fungal infections was of 14.3% and chemotherapy delays had a median of 20 days. Conclusions. It is of strict necessity to introduce efficient methods of prevention, diagnosis and treatment of invasive fungal infections in children with malignant hemopathies.*

Keywords: *invasive fungal infections, malignant hemopathies, intensive chemotherapy, neutropenia*

Rezumat: *Infecţiile fungice invazive reprezintă complicaţii infecţioase cu incidenţă în creştere şi care ridică numeroase probleme de diagnostic şi tratament la copii cu boli maligne. Scop. Analiza infecţiilor fungice invazive la copiii cu hemopatii maligne. Material şi metodă. Am efectuat o analiză retrospectivă a infecţiilor fungice invazive pe un lot de 132 pacienţii cu hemopatii maligne trataţi în Clinica Pediatrie II Cluj-Napoca în perioada 2001-2010. Rezultate. Incidenţa infecţiilor fungice invazive a fost de 9,8% din totalul episoadelor infecţioase. Corelaţii s-au observat între infecţiile fungice invazive, neutropenia severă prelungită (p 0,000) şi, respectiv, antibioterapie (p 0,000). Episoadele au fost diagnosticate ca "posibile" (60,7%),"probabile" (21,4%) şi "dovedite" (17,9%). Cei mai frecvente etiologii au fost Aspergillus şi Candida spp. Mortalitatea prin infecţii fungice invazive a fost de 14,3%, iar amânările de chimioterapie au avut o mediană de 20 de zile. Concluzii. Se impune introducerea unor metode eficiente de profilaxie, diagnostic şi tratament a infecţiilor fungice invazive la copiii cu hemopatii maligne.*

INTRODUCTION

In the last years, invasive fungal infections have become an ever increasing cause of morbidity and mortality in children with malignant hemopathies (1-4). Taking into account the difficulties encountered in assigning a diagnostic with certainty, the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC-IFIG/NIAID-MSG) developed an agreement in 2002, which was revised later on, in 2005. The afore-mentioned established the definition of invasive fungal infections, with a view to improve clinical and epidemiological trials, to support research in the field of new antimycotics and to set up new management strategies to fight against these infections (1,5).

Most invasive fungal infections are determined by Candida spp and Aspergillus spp, but species such as Rhizopus, Penicillium, Blastomyces are more frequently detected in immunodepressed patients (2,3,6,7). Prolonged and severe neutropenia, the administration of wide-range antibiotics, cortisonic therapy, aggressive chemotherapy and stem cell transplantation are widely-known risk factors in the onset of invasive fungal infections in children with malignant haemopathies (2-4,6). Despite advances made in early detection, by using specific screenings and imagery solutions, and despite advances made in the treatment, by introducing some new antimycotic agents, mortality caused by invasive fungal infections remains high. Moreover, preventive and empirical antimycotic therapy in risk patients is still considered as one of the most important factors in a successful management of these cases (2-4, 6-9).

OBJECTIVE

The objective of this paper is to present a retrospective analysis of the diagnostic, therapy and evolution of the invasive fungal infections in children with malignant haemopathies, treated in one oncopediatric unit only.

MATERIAL AND METHOD

We drafted a retrospective analysis of 132 patients with malignant hemopathies, diagnosed and treated in the Pediatric Oncology Department of the Pediatric Clinic no 2 Cluj-Napoca, during January 2001–December 2010, with an average medical observation period of 28 months. The lot of patients under analysis had the following diagnostic structure: 84 cases of acute lymphoblastic leukemia, 13 patients with acute

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myeloblastic leukemia, 15 children with nonHodgkin lymphoma and 20 cases of Hodgkin lymphoma. Patients were treated by international chemotherapy protocols: for acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML) and nonHodgkin lymphoma (NHL) successive versions of BFM protocols were applied for each type of malignity, and the protocols used for Hodgkin lymphoma (HL) were as follows: COPP/ABVD, DAL-HD 90 and GPOH-HD (the latter with two successive versions).

The data have been obtained by revising all medical sheets of patients included in this study. Data regarding the type of malignant hemopathy, the risk group, the stage of disease and the infectious episodes have also been collected. In patients diagnosed with invasive fungal infection (IFI) we analyzed: patient chemotherapy stage and if it entailed the administration of cortisone, lack or presence of neutropenia and its duration, previous administration of antibiotics, category of fungal infection, its etiology and location, assigned antimycotic therapy and possible toxic effects of the latter, evolution under treatment and alterations operated on chemotherapy protocols. Invasive fungal infections were categorized as "proven", "probable" and "possible", according to the agreement of 2005 concluded by the European Organization for Research and Treatment of the Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC-IFIG/NIAID-MSG) (5).

Statistical data were processed with the SPSS package. We applied the Chi-square for measuring the correlation and Cramer's Phi coefficient in order to find the correlation intensity.

RESULTS

We recorded 286 infectious episodes in our lot of patients. Up to 27 patients were recorded with 28 IFI episodes, meaning 9.8% of the total number of infections. All patients were under intensive chemotherapy when diagnosed with mycotic infection. 20 out of the 27 children, respectively 74%, manifested aggressive types of disease (medium or high risk for ALL, risk 2 for AML, stage III or IV for NHL, relapses of disease). No IFI cases were recorded in patients with Hodgkin lymphoma.

Severe neutropenia (< 500/mm^3), prolonged in time (average 14 days), was signalled at the time of the diagnosis or in the recent track record of the patient in 92.9% of the total number of IFI episodes (p 0.000). Other risk factors were also detected: corticotherapy (64.3% of the total number of episodes), wide-range antibiotherapy (64.3% of the total number of episodes, p 0.000) and reconstruction works of the hospital (14.9% of the total number of episodes). Characteristics of patients who developed IFI are shown in Table 1.

IFI were diagnosed as possible (60.7%), probable (21.4%) and proven (17.9%). Aspergillus spp was isolated in 4 episodes, Candida spp in 3 episodes; there were 2 infections with Rhyzopus spp and one case each for Penicillium marneffei and respectively Blastomyces dermatitidis, as etiological agents. IFI localization was pulmonary in 71.4%, systemic in 17.9%, cerebral in 7.1% and sinusal in 3.6% of the total number of episodes.

Healing was achieved in 24 episodes (i.e. 85.7%) following antimycotic therapy. For the two cases of mucormycosis with cerebral involvement, as well as for the patient with sinusal aspergillosis, combined therapy was used (medication and surgery). Both cases of mucormycosis were healed despite some neurological sequelae. The adverse effects of antimycotic therapy were rare in our lot: 3 patients presented dyselectrolitemia (two under Voriconazole treatment and one under Amphotericin B treatment) while another patient presented intolerance to Amphotericin B.

Table no. 1. Patient profile at the moment of diagnosis with invasive fungal infection

P	Diagnostic	Risk group/Stage	Chemotherapy	Neutrophils (/mm^3)	Length of neutropenia (days)	Cortisone	Previous antibiotic
1	ALL	Medium risk	Intensive	< 500	19	Yes	Yes
2	ALL	Standard risk	Intensive	< 1000	4	Yes	No
3	ALL	Relapse	Palliative	< 500	30	Yes	Yes
4	ALL	Medium risk	Intensive	< 500	12	Yes	Yes
5	ALL	Medium risk	Intensive	< 500	5	Yes	No
6	ALL	Medium risk	Intensive	< 500	7	Yes	No
7	ALL	Standard risk	Intensive	< 500	12	Yes	Yes
8	ALL	Standard risk	Intensive	< 500	2	Yes	No
9	ALL	Medium risk	Intensive	< 500	9	Yes	No
10	ALL	Medium risk	Intensive	< 500	10	No	No
11	ALL	Standard risk	Intensive	< 500	27	Yes	Yes
12	ALL	Standard risk	Intensive	< 500	8	No	No
13	ALL	High risk	Intensive	< 500	15	No	Yes
14	ALL	Medium risk	Intensive	< 500	38	Yes	Yes
15	ALL	Standard risk	Intensive	< 500	10	Yes	No
16	ALL	Medium risk	Intensive	< 500	15	Yes	Yes
			Intensive	> 1.500	-	Yes	No
17	ALL	High risk	Intensive	< 500	19	Yes	Yes
18	ALL	Relapse	Intensive	< 500	26	Yes	Yes
19	AML	Risk 2	Intensive	< 500	21	No	Yes
20	AML	Relapse	Intensive	< 500	14	No	Yes
21	AML	Risk 2	Intensive	< 500	12	No	Yes
22	AML	Risk 2	Intensive	< 500	28	No	Yes
23	AML	Risk 1	Intensive	< 500	12	No	Yes
24	NHL	Stage III	Intensive	< 500	6	No	No
25	NHL	Stage IV	Intensive	< 500	20	Yes	Yes
26	NHL	Stage IV	Intensive	< 500	16	No	Yes
27	NHL	Stage III	Intensive	< 500	16	Yes	Yes

Table no. 2. Invasive Fungal Infections: category, etiology, localisation, therapy, evolution

P	Category	Etiology	Location	Therapy	Evolution under therapy
1	Proven	Rhyzopus spp	Rhinocerebral mucormycosis	Amphotericin B	Healed with sequelae
2	Proven	Aspergillus flavus	Pulmonary	Voriconazole	Healed
3	Proven	Candida spp	Acute systemic	Voriconazole	Death
4	Possible	-	Pulmonary	Amphotericin B	Healed
5	Possible	-	Pulmonary	Voriconazole	Healed
6	Possible	-	Pulmonary	Voriconazole	Healed
7	Possible	-	Pulmonary	Voriconazole	Healed
8	Possible	-	Pulmonary	Voriconazole	Healed
9	Possible	-	Pulmonary	Voriconazole	Healed
10	Possible	-	Pulmonary	Voriconazole	Healed
11	Possible	-	Acute systemic	Fluconazole	Death
12	Possible	-	Pulmonary	Voriconazole	Healed
13	Possible	-	Acute systemic	Caspofungin, Voriconazole	Healed
14	Possible	-	Pulmonary	Voriconazole	Healed
15	Possible	-	Pulmonary	Voriconazole	Healed
16	Proven	Rhyzopus spp	Cerebral mucormycosis	Posaconazole	Healed with sequelae
	Possible	-	Pulmonary	Voriconazole	Healed
17	Proven	Candida parapsilosis	Acute systemic	Fluconazole	Death
18	Probable	Aspergillus spp	Pulmonary	Amphotericin B	Healed
19	Possible	-	Pulmonary	Amphotericin B	Healed
20	Possible	-	Pulmonary	Voriconazole, Caspofungin	Death
21	Probable	Aspergillus flavus	Pulmonary	Amphotericin B	Healed
22	Proven	Aspergillus spp	Sinusal	Voriconazole	Healed
23	Possible	-	Pulmonary	Voriconazole	Healed
24	Probable	Penicillium marneffei	Pulmonary	Voriconazole	Healed
25	Probable	Blastomyces dermatitidis	Pulmonary	Ketoconazole	Healed
26	Probable	Candida albicans	Acute systemic	Fluconazole	Healed
27	Possible	-	Pulmonary	Voriconazole	Healed

The data regarding the category, the etiology, the location, the antimycotic therapy and the evolution under treatment of the IFI episodes are presented in table 2.

IFI was considered responsible for the death of four patients (14.3% of the episodes), two of which had also been diagnosed with a progressive malignant condition with no response to chemotherapy. The IFI episodes determined a total delay of 455 days of the cytostatic protocols, with an average of 20 days.

DISCUSSIONS

Although bacterial infections are still the most common infectious complications in patients with malignant hemopathies, the frequency of fungal infections has increased considerably (4, 10-14). The incidence of 9.8% of IFI in pediatric patients with malignant hemopathies recorded in our study is similar to the data reported by the literature which indicates incidences varying from 0-20% (3, 6-8, 11, 13, 15).

Our study confirms previous observations which emphasised that the aggressiveness of chemotherapy is one of the most important favouring factors in the onset of invasive fungal infections (1-3,6). Within our lot, all episodes of IFI were registered in patients who were undergoing intensive chemotherapy. Furthermore, 74% of the children had severe disease forms which required an increased aggressiveness of the chemotherapy. An additional aspect which indicates the close link between the intensity of chemotherapy and IFI is the fact that we have not registered any such episodes in patients with Hodgkin lymphoma, a malignant hemopathy that uses less aggressive cytostatic protocols.

Severe and long-lasting neutropenia has proven to be a risk factor statistically correlated with the IFI episodes (p 0,000). In our study, neutropenia under 500/mm^3 with an average lasting period of 14 days, was present in 92.9% of the fungal infections. Our observations matched the observations of other clinical studies, according to which many infections occurred in patients with previous severe neutropenia at the end of bone marrow aplasia, which was marked by the increase of the number of leukocytes. Unlike other studies, our study has not indicated that corticotherapy (applied in 64.3% of the cases) is statistically linked to invasive fungal infection episodes. Broad spectrum antibiotherapy, however, proved to be a high risk factor (p 0,000) for the onset of severe mycotic infections in our patients (1-3, 6, 11, 12, 15). All 4 cases of pulmonary aspergillosis (3 probable and one possible) also correlated with the refurbishing activities performed within the hospital which the literature acknowledges as one of the risk factors associated with Aspergillus spp infections in immunosupressed patients (3, 16, 17).

We have managed to specify the etiology in 39.3% of the episodes, with 17.9% labelled as proven IFI and 21.4% as probable. For the majority of episodes (60.7%), the diagnosis was established based only on clinical-radiological criteria and on the presence of favouring factors related to the host, according to the EORTC-IFIG/NIAID-MSG consensus. This indicates the difficulty in diagnosing invasive fungal infection and the need to use specific and sensitive methods which allow an early and correct diagnosis in high risk patients, such as children with malignant hemopathies. The recent introduction in the IFI diagnostic algorithm of serum determination of galactomannan and β-D-glucan (components of the fungus cellular wall), as well as of CT and MRI examinations, have led

to a more accurate diagnosis.

Following the pattern described in the specialised literature, the most frequent infections registered in our study were due to Aspergillus spp and Candida spp (4 and 3 cases respectively) (1-3, 6-8, 12-15). The lower incidence of Candida spp infections may be explained through the prophylaxis with Fluconazole applied in several cases, however, since this prophylaxis has not been carried out by complying with a rigorous protocol, it could not be properly analysed in this paper. Similarly to other studies, the majority of the IFI in our patients were pulmonary infections. The cerebral involvement was only present in the cases of infections with Rhyzopus spp, whereas the sinusal infection was registered in two episodes, one of rhinocerebral mucormycosis and the other of sinusal aspergillosis.

The applied antimycotic therapy varied according to the result of the fungigram when the etiological agent was isolated through culture. In the cases of possible fungal infection, lacking the mycological diagnosis, the therapy was empirical, the only selection criterion being the recognised sensibility of the suspected fungus. Unlike other studies have indicated, the adverse effects registered in the children of our cohort were rare and mild: there were 3 cases of hypopotassemia (two under Voriconazole and one under Amphotericin B), which required the administration of additional intravenous potassium and one case of intolerance to the increased dose of Amphotericin B (the patient experienced shivers, pallor and tachicardia) which determined the maintenance of the low dosage treatment (0.7 mg/kg/day) (2, 18). Three patients, according to the indications of the therapeutical protocols, also required surgery in addition to the antimycotic therapy: the extirpation of the cerebral abscesses in the patients with murcomycosis and ORL intervention consisting of ethmoidectomy and antrostomy in the patient with sinusal aspergillosis (19). Both patients with cerebral mucormycosis were left with sequelae - one of the children developed spastic hemiplegia and the other epilepsy

We registered a mortality rate of 14.3% due to IFI in our study which is consistent with the data reported in the specialised literature. Two of the deceased patients showed relapses of the disease and did not respond to chemotherapy, which of course, contributed in a great extent to their death. Although the IFI had a decreased mortality rate, they had a major impact upon the protocolar discipline, causing an impressive total delay of 455 days of the chemotherapy protocol, the average period being of 20 days (1-4, 6, 9, 12, 15).

CONCLUSIONS

Invasive fungal infections are becoming an ever increasing cause of morbidity and mortality in pediatric patients with malignant haemopathies. It is thus necessary to introduce new efficient prophylaxis, diagnosis and treatment methods in order to successfully manage these infectious complications.

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