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Invasive aspergillosis in patients with hematological malignancies in the Czech and Slovak republics: Fungal InfectioN Database (FIND) analysis, 2005–2009

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SUMMARY

Objectives: To evaluate risk factors, diagnostic procedures, and treatment outcomes of invasive aspergillosis (IA) in patients with hematological malignancies.
Methods: A retrospective analysis of data from proven/probable IA cases that occurred from 2005 to 2009 at 10 hematology centers was performed.
Results: We identified 176 IA cases that mainly occurred in patients with acute leukemias (58.5%), mostly those on induction/re-induction treatments (39.8%). Prolonged neutropenia was the most frequent risk factor for IA (61.4%). The lungs were the most frequently affected site (93.8%) and computed tomography detected abnormalities in all episodes; however, only 53.7% of patients had findings suggestive of IA. Galactomannan (GM) detection in serum or bronchoalveolar lavage fluid (positive in 79.1% and 78.8% of episodes, respectively) played a crucial role in IA diagnosis. Neutrophil count and antifungal prophylaxis did not influence the GM positivity rate, but empirical therapy decreased this rate (in serum). Of the IA cases, 53.2% responded to initial antifungal therapy. The combination of voriconazole and echinocandin, even as initial or salvage therapy, did not perform better than voriconazole monotherapy ($p = 0.924$ for initial therapy and $p = 0.205$ for salvage therapy). Neutrophil recovery had a significant role in the response to initial (but not salvage) antifungal therapy.
Conclusions: Our retrospective analysis identified key diagnostic and treatment characteristics, and this understanding could improve the management of hematological malignancy patients with IA.

1. Introduction

Invasive fungal diseases (IFD) are an important cause of morbidity and mortality in patients with hematological diseases.[1,2] The epidemiology of IFD in this group of severely immunocompromised patients has changed substantially during the last two decades, with invasive aspergillosis (IA) being a predominant infection.[1] The incidence of this infection can vary and is mainly based on the underlying hematological malignancy; it can reach up to 10% among patients undergoing treatment for acute leukemia or allogeneic hematopoietic stem cell transplantation (HSCT).[3] However, there have been several key advancements over the past decade that have significantly improved not only the diagnosis (widespread availability of high-resolution computed tomography (HRCT) and non-culture based diagnostic tools, such as the detection of galactomannan (GM)), but also treatment

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options (availability of new antifungal drugs, e.g., voriconazole and echinocandins) of IA. These events have led to the recently reported improvement in the prognosis of patients with this life-threatening infection.[2,4,5] Moreover, several observational registries in Europe, as well as worldwide, have been created with the goal of collecting real world data regarding incidence, risk factors, and treatment outcomes of patients with IA.[1,2,4–6]

In this multicenter study, we report data from IA episodes that occurred in patients with hematological malignancies. These data were retrospectively collected from the Fungal InfectioN Database (FIND), which holds data from almost all hematology centers in the Czech and Slovak republics. The aim of this study was to analyze the risk factors, diagnostic procedures, and treatment outcomes from the largest cohort of IA episodes in Central Europe published to date.

2. Methods

2.1. Design

Thirteen hematology centers in the Czech and Slovak republics participate in the FIND project. The database consists of retrospectively collected data of proven and probable IA cases that occurred between 2001 and 2009, as well as a prospective collection of cases from 2010 onwards.

This study was conducted by performing an analysis of proven and probable IA cases that occurred between January 1, 2005 and December 31, 2009, which had been retrospectively entered as electronic case report forms by 10 of 13 participating centers (seven adult and three pediatric centers). The distribution of episodes during this time period was not uniform and was mainly dependent on the extension of non-culture-based diagnostic techniques (e.g., GM detection) among centers. Therefore, the number of episodes in individual time intervals does not reflect the real incidence of infection. Forty-one percent of cases entered into the database and analyzed occurred between 2005 and 2007, 59% between 2008 and 2009.

2.2. Case identification

Cases were identified in participating centers by reviewing the patient charts as well as laboratory, microbiology, and imaging results. Pathology reports from autopsies were also used. All identified episodes of IA during the observation period were included in the database.

The variables collected in the electronic case report forms included the subject's demographic characteristics, underlying hematological malignancy and treatment, clinical signs and symptoms, and the results of microbiological and histological investigations, as well as results of imaging studies, information regarding the use of mold-active antifungal prophylaxis and empirical antifungal treatment, targeted antifungal treatment and outcomes, neutrophil counts at the time of diagnosis as well as before and after each antifungal treatment, and finally patient survival. Due to the retrospective design of this study, a patient's informed consent was not required. The Institutional Review Board of the University Hospital Brno approved this study.

2.3. Definitions

Episodes of IA were defined according to the 2002 European Organisation for Research and Treatment of Cancer and Mycosis Study Group (EORTC/MSG) criteria.[7] The day of diagnosis was defined as the day when criteria for proven or probable IA were fulfilled. Empirical antifungal therapy was defined as the administration of systemic antifungal treatment in patients with persistent fever only, or in patients who did not fulfill criteria for proven or probable IFD at the time of treatment initiation. Targeted antifungal therapy was started when patients fulfilled criteria for proven or probable IA. The overall outcome of therapy, as well as the outcome of each line of antifungal treatment, was classified according to published EORTC/MSG recommendations.[8] The effect of therapy was evaluated only if the targeted antifungal therapy lasted at least 5 days. An independent, blinded evaluation of all the entered data was performed by a review board at the main study center, with special consideration to the fulfillment of EORTC/MSG criteria for the diagnosis of proven or probable IA, as well as treatment outcome.

2.4. Statistical analysis

Frequency tables and standard descriptive statistics were used for summation of the patient characteristics. Proportions were compared with the maximum-likelihood Chi-square test or Fisher's exact test. Continuous variables were compared with the Mann–Whitney or Kruskal–Wallis analysis of variance

Table 1
Baseline characteristics

Patients	
No. of patients	176
Age, years, median (range)	56 (3–77)
Sex, male/female, *n* (%)	104 (59.1%)/ 72 (40.9%)
Patient's disease at baseline, *n* (%)	
AML + MDS	73 (41.5%)
ALL	30 (17.0%)
NHL + HL	27 (15.3%)
CLL	20 (11.4%)
MM	12 (6.8%)
CML + CMPD	4 (2.3%)
Other	10 (5.7%)
Anticancer therapy during/before IA, *n* (%)	
Induction/reinduction therapy of acute leukemia	70 (39.8%)
Allogeneic HSCT	30 (17.0%)
Autologous HSCT	17 (9.7%)
Other	52 (29.5%)
None	7 (4.0%)
Presence of risk factors for development of IA, *n* (%)	
Neutropenia $<0.5 \times 10^9$/l for >10 days	108 (61.4%)
Administration of corticosteroids for >21 days	50 (28.4%)
Pulmonary/respiratory tract disease in anamnesis (COPD, etc.)	22 (12.5%)
GVHD	20 (11.4%)
Other risk factors	41 (23.3%)
Number of risk factors present at diagnosis, *n* (%)	
0	29 (16.5%)
1	79 (44.9%)
2	44 (25.0%)
≥3	24 (13.6%)
IA episodes	
No. of episodes	176
Certainty of diagnosis according to EORTC/MSG 2002 criteria, *n* (%)	
Proven IA	27 (15.3%)
Probable IA	149 (84.7%)
Site of infection, *n* (%)	
Lung	165 (93.8%)
Sinuses	1 (0.6%)
Disseminated	7 (4.0%)
Other	3 (1.7%)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMPD, chronic myeloproliferative disease; COPD, chronic obstructive pulmonary disease; EORTC/MSG, European Organisation for Research and Treatment of Cancer/Mycoses Study Group; GVHD, graft-versus-host disease; HL, Hodgkin lymphoma; HSCT, hematopoietic stem cell transplantation; IA, invasive aspergillosis; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.