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Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil

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Abstract

Invasive fungal disease (IFD) shows distinct regional incidence patterns and epidemiological features depending on the geographic region. We conducted a prospective survey in eight centres in Brazil from May 2007 to July 2009. All haematopoietic cell transplant (HCT) recipients and patients with acute myeloid leukaemia (AML) or myelodysplasia (MDS) were followed from admission until 1 year (HCT) or end of consolidation therapy (AML/MDS). The 12-month cumulative incidence (CI) of proven or probable IFD was calculated, and curves were compared using the Grey test. Among 237 AML/MDS patients and 700 HCT recipients (378 allogeneic, 322 autologous), the 1-year CI of IFD in AML/MDS, allogeneic HCT and autologous HCT was 18.7%, 11.3% and 1.9% ($p < 0.001$), respectively. Fusariosis (23 episodes), aspergillosis (20 episodes) and candidiasis (11 episodes) were the most frequent IFD. The 1-year CI of aspergillosis and fusariosis in AML/MDS, allogeneic HCT and autologous HCT were 13.4%, 2.3% and 0% ($p < 0.001$), and 5.2%, 3.8% and 0.6% (p 0.01), respectively. The 6-week probability of survival was 53%, and was lower in cases of fusariosis (41%). We observed a high burden of IFD and a high incidence and mortality for fusariosis in this first multicentre epidemiological study of IFD in haematological patients in Brazil.

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Introduction

Invasive fungal disease (IFD) represents a major complication in patients with haematological malignancies and in haematopoietic cell transplant (HCT) recipients [1,2]. The incidence and epidemiology of such infections have been characterized in various retrospective studies [3–17] and a few prospective studies [18–22] conducted in Europe, the USA and Japan. However, the incidence and epidemiology of IFD may differ significantly depending on the geographic region. The knowledge of these epidemiological differences is important to implement appropriate strategies of prevention, diagnosis and therapy, and also because of the globalization of the world, with frequent travelling and migration.

In this paper we report the results of a study that involved patients with acute myeloid leukaemia (AML) or myelodysplasia (MDS) receiving intensive chemotherapy and HCT recipients from eight major referring centres.

Patients and Methods

This is a prospective multicentre cohort study in eight centres located in seven cities in the south and south-east of

Brazil. These centres are representative of a substantial proportion of public hospitals performing HCT in Brazil. Between May 2007 and July 2009, all HCT recipients and all patients with AML or MDS undergoing induction chemotherapy for newly diagnosed or relapsed disease were followed prospectively. Patients receiving palliative care or non-myelotoxic induction remission regimens were excluded. The study was approved by the Institutional Review Board of each participating centre.

At each centre, one investigator prospectively registered all new patients with a diagnosis of AML/MDS and all HCT recipients, followed them throughout the entire period of observation, and electronically sent data for each phase of the treatment, until the end of observation. We recorded demographic data, underlying disease, chemotherapeutic regimens, and for the HCT cohort, details of the transplant were also recorded, including type of transplant (autologous or allogeneic), donor (family-related or unrelated), human leucocyte antigen (HLA) matching (matched, mismatched, i.e. with some HLA disparity), stem cell source (peripheral blood, bone marrow or cord blood), and conditioning regimen (myeloablative or non-myeloablative).

All centres had high-resolution computed tomography and automated blood culture systems. Routine serum galactomannan testing was available only during the last 13 months of the study. The application of the test (as screening or diagnostic tool) was at the discretion of each centre. If patients from any of the two cohorts developed an IFD, they was followed for 3 months, and details of the IFD were recorded, including clinical manifestations, diagnostic criteria, aetiology, treatment and the outcome. If a patient developed more than one episode of IFD, only the first episode was considered in the analysis. The cases of IFD were classified by the local investigators, and blindly reviewed and classified by a data review committee, as proven or probable IFD, according to the modified European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) criteria [23]. Briefly, proven cases required either a positive culture from a normally sterile fluid or tissue (urine excluded) or visualization of fungi in tissue, whereas probable cases were defined on the basis of host factors, clinical features and mycological criteria. Cases of possible IFD were excluded.

Patients in the AML/MDS cohort were followed from the start of the induction remission chemotherapy until the end of consolidation therapy. Typical duration of neutropenia in the induction and consolidation phases is 3–4 weeks and 1–2 weeks, respectively. If the patient was to receive HCT as consolidation therapy then the patient was censored at that time, and entered as a new disease episode in the HCT cohort. In case of relapse or death for a cause not related to IFD before the end of consolidation therapy, observation was interrupted and the patient's status was recorded as having had a competing event.

Patients in the HCT cohort were followed from conditioning until 1 year post-transplant. If a patient needed to receive a second HCT, then the patient was censored at that point, and re-entered in the study as a new disease episode in the HCT cohort. Except for age and gender, all data are expressed per disease episode. Relapse of the underlying disease or death from causes not related to IFD were recorded as competing events.

Patients were managed according to the routine of each centre. Neutropenia was defined as an absolute neutrophil count $<0.5 \times 10^3/\mu L$ and neutrophil recovery as an absolute neutrophil count $\geq 0.5 \times 10^3/\mu L$ on three consecutive days.

We calculated the cumulative incidence (CI) of IFD, using time to first IFD, defined as the date of diagnosis of IFD minus the first date in the cohort. The date of the diagnosis of IFD was defined as the date of the first clinical documentation of infection; if the diagnosis was obtained post mortem, the date of death was recorded as the date of diagnosis of IFD. For the calculation of the CI, we considered relapse of the underlying disease and death from causes not related to IFD as competing events. The Grey test was used for comparison between curves. One-year survival was calculated using the Kaplan–Meier method and the curves were compared with the log rank test. We used the CMPRISK package (R, version 2.14.1) to calculate CI, and the SPSS package (SPSS, Inc., Chicago, IL version 15.0) for the other analyses.

Results

Characteristics of the patients

During the study period a total of 954 disease episodes were registered in the database. Eleven disease episodes in the AML/MDS cohort and six in the HCT cohort were excluded because of incomplete data. We therefore analysed 937 disease episodes: 237 induction remission courses of AML/MDS (in 202 patients) and 700 HCTs (in 673 patients). The median age of the 875 patients was 37 years (0–82 years), and 56% were male. As shown in Table 1, the most frequent underlying disease among allogeneic HCT recipients was AML, followed by acute lymphoid leukaemia, whereas multiple myeloma accounted for 47.5% of autologous HCT. Most allogeneic HCTs were myeloablative (80.4%), from a matched related donor (71.7%), with the bone marrow as the stem cell source (56.1%).

TABLE 1. Characteristics of 937 disease episodes in the cohort

Variable	HCT *n* = 700		AML/MDS *n* = 237	Total *n* = 937
	Allogeneic *n* = 378	Autologous *n* = 322		
Underlying disease, *n* (%)				
AML	86 (22.8)	10 (3.1)	230 (97.0)	326 (34.8)
MDS	25 (6.6)	–	7 (3.0)	32 (3.4)
Multiple myeloma	7 (1.9)	153 (47.5)	–	160 (17.1)
Hodgkin's lymphoma	11 (2.9)	63 (19.6)	–	74 (7.9)
Acute lymphocytic leukaemia	70 (18.5)	1 (0.3)	–	71 (7.6)
Non-Hodgkin lymphoma	18 (4.8)	50 (15.5)	–	68 (7.3)
Aplastic anaemia	56 (14.8)	–	–	56 (6.0)
Other[a]	105 (27.7)	45 (14.0)	–	150 (15.9)
Type of allogeneic HCT, *n* (%)				
Matched, related	271 (71.7)	–	–	–
Matched, unrelated	14 (3.7)	–	–	–
Mismatched, related	55 (14.6)	–	–	–
Mismatched, unrelated	30 (10.1)	–	–	–
Stem cell source, *n* (%)				
Peripheral blood	128 (33.8)	312 (96.9)	–	440/700 (62.9)
Bone marrow	212 (56.1)	10 (3.1)	–	222/700 (31.7)
Cord blood	38 (10.1)	–	–	38/700 (5.4)
Conditioning regimen, *n* (%)[b]				
Myeloablative	304 (80.4)	302 (93.8)	–	606/700 (86.6)
Non-myeloablative	74 (19.6)	20 (6.2)	–	94/700 (13.4)
Induction regimen for AML/MDS, *n* (%)				
First induction	–	–	188 (79.3)	–
Relapse	–	–	49 (20.7)	–
Hospitalized in a room with HEPA filter, *n* (%)	263 (69.6)	249 (77.3)	86 (36.3)	598 (63.8)
Antifungal prophylaxis, *n* (%)	338 (89.4)	235 (73.0)	133 (56.1)	706 (75.3)
Fluconazole	308 (81.5)	235 (73.0)	125 (52.7)	
Itraconazole	2 (0.5)	–	5 (2.1)	7 (0.7)
Voriconazole	14 (3.7)	–	3 (1.3)	17 (1.8)
d-AMB	14 (3.7)	–	–	14 (1.5)
Duration (days) of neutropenia, median (range)	15 (2–57)	9 (6–39)	19 (6–86)	12 (2–86)
Duration (days) of follow-up, median (range)	103 (2–365)	103 (11–365)	97 (1–365)	102 (1–365)

HCT, haematopoietic cell transplantation; AML, acute myeloid leukaemia; MDS, myelodysplasia; HEPA, high-efficiency particulate air; d-AMB, deoxycholate amphotericin B.
[a]Other underlying diseases—Allogeneic HCT: Fanconi anaemia (27), other bone marrow failure syndromes (11), chronic myeloid leukaemia (27), other myeloproliferative disease (11), congenital immunodeficiency (14), congenital metabolic disease (6), chronic lymphocytic leukaemia (6), and solid tumour, sickle cell anaemia and Langerhans cell histiocytosis (1 each); Autologous HCT: autoimmune disease (27), solid tumour (17), Langerhans cell histiocytosis (1).
[b]Conditioning regimen: allogeneic HCT—most patients with AML received busulfan + cyclophosphamide (48%) or busulfan + fludarabine (24%) and most patients with acute lymphocytic leukaemia received cyclophosphamide + total body irradiation (49%) or + busulfan (30%); autologous HCT—most patients with lymphoma received carmustine + melphalan + etoposide + cytarabine (61%) or cyclophosphamide + etoposide + carmustine (18%) and most patients with myeloma received melphalan (96%).

Invasive fungal diseases

During the study period a total of 108 episodes of IFD were diagnosed, 66 of which (61%) were proven or probable. Table 2 shows the classification and aetiology of the 66 proven or probable IFD. Invasive fusariosis was the leading IFD (23 episodes, including three mixed infections), followed by aspergillosis (20 episodes, including one mixed infection), invasive candidiasis (11 episodes, including one mixed infection) and hyalohyphomycosis (eight episodes). Only three cases of mucormycosis were diagnosed, all in allogeneic HCT recipients.

Incidence and outcome of invasive fungal disease

The 1-year CI of all IFD in the entire cohort was 8.7%, and varied from 4.7% to 24.2% in the eight centres. The CI of the different aetiologies of IFD varied among the eight centres. Two centres did not report any case of invasive aspergillosis (IA), whereas in two the CI was >7%. Fusariosis was reported in all but two centres, with five centres reporting CI >3%. Candidiasis was reported in four centres and mucormycosis in three.

The 1-year CI of all IFD differed according to patient's age: 6.5% in patients <18 years, 8.4% in patients aged 19–60 years, and 14.4% in patients >60 years old (p 0.03). As shown in Fig. 1, the 1-year CI of all IFD was 18.7% in AML/MDS and 7.2% in HCT (11.3% in allogeneic HCT and 1.9% in autologous HCT, p <0.001). The 1-year CI of IA in AML/MDS, allogeneic HCT and autologous HCT was 13.4%, 2.3% and 0%, respectively (p <0.001) (Table 3). No significant differences were observed in the incidence of IA in the periods before and after the availability of serum galactomannan in the centres.

The 6-week probability of survival from diagnosis of IFD was 53% overall. The 6-week probability of survival in patients with candidiasis, IA and fusariosis was 70%, 63% and 41%, respectively.

Table 4 shows the timing of the occurrence of IFD in the three cohorts. In the AML/MDS cohort, the median time from chemotherapy to onset of IFD was 15 days (32–192 days). The 1-year CI of IFD was not different between patients receiving chemotherapy as first induction or for the treatment of relapse (20.1% vs 16.6%, respectively, p 0.76). The median time from HCT to IFD was 14 days (11–233) in the autologous cohort, and 53 days (19–232) in the allogeneic cohort (p 0.03). The 1-year CI of IFD in matched

TABLE 2. Classification and aetiology of 66 proven and probable invasive fungal diseases by underlying condition

	HCT *n* = 700			
Invasive fungal disease	**Allogeneic *n* = 378 (%)**	**Autologous *n* = 322 (%)**	**AML/MDS *n* = 237 (%)**	**Total *n* = 937 (%)**
Proven	28 (7.4)	5 (1.5)	20 (8.4)	53 (5.6)
Fusariosis	11 (2.9)	2 (0.6)	6 (2.5)	19 (2.0)
Candidiasis	6 (1.6)	2 (0.6)	2 (0.8)	10 (1.1)
Hyalohyphomycosis	4 (1.0)	–	4 (1.7)	8 (0.1)
Aspergillosis	1 (0.3)	–	8 (3.4)	9 (1.0)
Mucormycosis	3 (0.8)	–	–	3 (0.3)
Other[a]	3	1	–	4
Probable	7 (1.8)	–	6 (2.5)	13 (1.4)
Aspergillosis	6 (1.6)	–	4 (1.7)	10 (1.1)
Fusariosis[b]	1 (0.3)	–	–	1 (0.1)
Other[c]	–	–	2	2
Total	35 (9.2)	5 (1.5)	26 (11.0)	66 (7.0)

HCT, haematopoietic cell transplantation; AML, acute myeloid leukaemia; MDS, myelodysplasia.
[a]Other invasive fungal diseases: cryptococcosis (1, autologous HCT), candidaemia + fusariosis (1, allogeneic HCT), fusariosis + infection due to *Colletotrichum* sp. (1, allogeneic HCT), infection due to *Rhinocladiella acquaspersa* (1, allogeneic HCT).
[b]Probable fusariosis diagnosed in a patient with typical skin lesions and hyaline hyphae on direct examination and histopathology of skin biopsy but negative culture.
[c]Other invasive fungal diseases: aspergillosis + fusariosis (1, AML/MDS), infection due to *Geotrichum* sp. (1, AML/MDS) Total episodes: fusariosis 23, aspergillosis 20, candidiasis 11, mucormycosis 3. Species distribution: Fusariosis—*Fusarium solani* complex (16), *Fusarium oxysporum* complex and *Fusarium incarnatum* (1 each), *Fusarium* species 5; Candidaemia—*Candida albicans* and *Candida parapsilosis* (3 each), *Candida guilliermondii* (2), and *Candida tropicalis*, *Candida krusei* and *Candida famata* (1 each); Aspergillosis—*Aspergillus flavus* (4), *Aspergillus fumigatus* (1); 15 cases were diagnosed by positive serum (6) or serum + bronchoalveolar lavage (1) galactomannan antigen, direct exam (1) or biopsy (7).

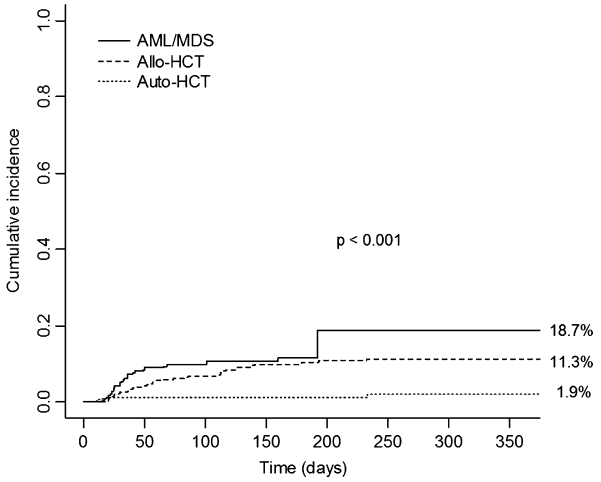

FIG. 1. Cumulative incidence of invasive fungal disease in 237 patients with acute myeloid leukaemia/myelodysplasia, and 378 allogeneic and 322 autologous haematopoietic cell transplant recipients. AML/MDS, acute myeloid leukaemia/myelodysplasia; Allo-HCT, allogeneic haematopoietic cell transplantation; Auto-HCT, autologous haematopoietic cell transplantation.

related, matched unrelated, mismatched related and mismatched unrelated allogeneic HCT was 11.3%, 9.1%, 7.1% and 16.4%, respectively (p 0.74).

Discussion

In this first prospective multicentre epidemiological study of IFD in haematological patients in Latin America, we found a high burden of IFD in both the AML/MDS and the HCT cohorts; invasive fusariosis was the leading IFD, followed by IA.

The incidence of IFD in the present study was expressed as CI with competing events because this is an appropriate measure of incidence in a cohort with different durations of observation and various competing risks [24]. Two studies reported the incidence of IFD in a similar fashion. In a retrospective single-centre study in Japan [9], the 3-year CI of IA among allogeneic HCT recipients was 5.6%. In the other study (TRANSNET), prospective data on all HCT performed in 21 centres in the USA were collected for a period of approximately 3 years. The 1-year CI of proven + probable disease was 3.4%, contrasting with the 7.2% CI in the present study [19]. This difference is mostly a result of the higher incidence of fusariosis in our allogeneic HCT cohort (5.2%), because the CI of IA (2.3% in our cohort and 1.6% in the other study) was similar.

We did not observe differences in the CI of IFD between children and younger adults, but a higher incidence was observed in patients older than 60 years. The higher CI of IFD in this age group may be related to poor response to induction chemotherapy in the AML/MDS cohort, and high transplant-related toxicity, both of which occur in a much higher proportion of this age group [25,26].

We observed a high CI of IFD in the AML/MDS cohort, mainly IA and fusariosis. In a prospective study in 17 centres in Italy, 93 IFD (12.4%) were diagnosed in 747 adults with AML, 86% of which were caused by moulds [20]. A retrospective study from the same group reported a prevalence of 12% of IFD in patients with AML (2.7% prevalence of IA)

TABLE 3. Cumulative incidence (1-year) of invasive fungal diseases by underlying condition

	Allogeneic HCT	Autologous HCT	AML/MDS	Total (%)
Fusariosis*	5.2 (%)	0.6 (%)	3.8 (%)	
Aspergillosis**	2.3	–	13.4	
Candidiasis	2.4	0.6	1.7	
Mucormycosis		–	–	
All IFD	11.3	1.9	18.7	8.7

HCT, haematopoietic cell transplantation; AML, acute myeloid leukaemia; MDS, myelodysplasia; IFD, invasive fungal disease.
*p 0.01; **p <0.001.

TABLE 4. Timing of occurrence of invasive fungal diseases by underlying condition

Cohort	No. of cases		
AML/MDS	Induction	Consolidation	–
Aspergillosis	11	1	–
Candidiasis	1	1	–
Fusariosis	6	–	–
Other	6	–	–
Allogeneic HCT	Day 0 to day +30	Day +31 to day +100	Day +100 to day +365
Aspergillosis	2	1	4
Candidiasis	1	4	2
Fusariosis	5	6	3
Mucormycosis	1	2	–
Other	3	3	1
Autologous HCT	Day 0 to day +30	Day +31 to day +100	Day +100 to day+365
Aspergillosis	–	1	–
Candidiasis	2	–	–
Fusariosis	2	1	–
Other	–	–	1[a]

AML, acute myeloid leukaemia; MDS, myelodysplasia; HCT, haematopoietic cell transplantation.
[a]Cryptococcosis diagnosed on day 233 in a patient with multiple myeloma.

[16]. In another retrospective study, the prevalence of IFD was 6.7% [11]. Contrary to what we would expect, there were no differences in the CI between AML patients in first induction and in relapse, but this may be because of the small number of relapsed patients in the present study.

We observed a large difference in the CI of IFD between patient with AML/MDS and those with allogeneic HCT, mostly because of a higher incidence of IA in the AML/MDS cohort. The Brazilian public health system reimburses much less money for AML compared with HCT, which has a separate programme and funding. As a consequence, for example, AML patients are typically cared for in double-bed rooms without HEPA (high-efficiency particulate air) filters whereas allogeneic HCT recipients are cared for in single-bed rooms with HEPA filters and positive pressure. Another possible reason for these differences is the fact that HCT is usually an elective procedure in which patients are carefully selected, whereas patients with AML/MDS represent an unselected population. Finally, the lower incidence in HCT could be a result of an increase in non-myeloablative transplants and the use of peripheral blood stem cells, typically associated with shorter duration of neutropenia, as opposed to the typical more than 3-week duration of neutropenia that follows induction remission for AML/MDS.

The time of occurrence of IFD in the present study showed a typical pattern in which most cases were diagnosed during the period of neutropenia of induction chemotherapy in the AML/MDS cohort and in autologous HCT recipients, and was distributed throughout the post-transplant period in allogeneic HCT, as previously reported [12,13,27].

A remarkable finding of our study was the high 1-year CI of invasive fusariosis. The TRANSNET study reported 1-year CI <0.3% for all mould infections [19], and an Italian retrospective study reported only three cases of fusariosis among 1249 allogeneic HCT recipients (0.2% prevalence) [16], compared with 3.7% in the present study. In a previous study we reported a prevalence of 0.6% among HCT recipients between 1985 and 2001 [28]. The data presented here suggest, therefore, that the incidence of fusariosis in HCT recipients has increased in Brazil. The same was observed in the AML population, with 3.4% of fusariosis compared with 0.2% in Italy [15]. A centre effect for the high incidence of invasive fusariosis is unlikely because only two centres did not report any case of fusariosis, and the 1-year CI was >3% in five centres. An investigation in one of the centres showed that in addition to invasive fusariosis in immunocompromised patients, there had been an increase in the incidence of superficial infections in outpatient immunocompetent individuals, suggesting that an increase in environmental reservoirs of *Fusarium* have occurred in the region (Nucci *et al.*, submitted).

We found only three cases of mucormycosis, all occurring in the allogeneic HCT cohort (1-year CI of 0.4%). This is in contrast with the results of the TRANSNET study that reported a prevalence of 8% among HCT recipients [19], but is in accordance with the results of an Italian study, reporting only one case among 1249 allogeneic HCT recipients [16]. These data illustrate that differences in the incidence of IFD in different regions of the globe are expected, and may be caused by multiple factors including patients at risk, degrees of immunosuppression and local environmental factors.

A limitation of the present study is the fact that galactomannan testing, an important diagnostic tool for IA [29], was not routinely performed for most of the period of data collection. This may have underestimated the incidence of IA. Indeed, most of the 42 possible IFD diagnosed in the study period, and not reported in the present paper, were 'possible IA', i.e. patients with well-circumscribed lung infiltrates but without microbiological confirmation of IA. In addition,

the way each centre used the test (as screening or to confirm the diagnosis) may have influenced the CI of IA.

Our results have important clinical and research implications. Given the high incidence of IFD in AML/MDS patients, antifungal prophylaxis with a mould-active azole such as posaconazole seems justifiable [30]. Alternatively, active monitoring with serial (>2×/week) serum galactomannan and images may help to diagnose these infections early, with a potential for improving the outcome [31]. In addition, studies (ongoing) are needed to better characterize the epidemiology of invasive fusariosis, considering its high incidence in the region.

We conclude that IFD has a high incidence and mortality in patients with AML/MDS and in HCT recipients in Brazil. Fusariosis and IA are the leading mycoses, and the incidence of mucormycosis is low.

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Transparency Declaration

The authors declare no conflict of interest.

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