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Mucormycosis in hematologic patients

LIVIO PAGANO
MASSIMO OFFIDANI
LUANA FIANCHI
ANNAMARIA NOSARI
ANNA CANDONI
MARCO PICCARDI
LAURA CORVATTA
DOMENICO D'ANTONIO
CORRADO GIRMENIA
PIETRO MARTINO
ALBANO DEL FAVERO
FOR THE GIMEMA (GRUPPO ITALIANO MALATTIE EMATOLOGICHE DELL'ADULTO) INFECTION PROGRAM

A B S T R A C T

Background and Objectives. To evaluate the clinical characteristics of patients affected by hematologic malignancies who developed mucormycosis and to ascertain the factors which influenced the outcome following mycotic infection.

Design and Methods. This was a retrospective study conducted over a 15-year period (1987-2001). The study included 59 patients with hematologic malignancies with a proven or probable mucormycosis admitted in 18 Hematology Divisions in tertiary care or university hospitals.

Results. The most frequent sites of infection were lung (64%) and orbito-sinus-facial (24%); cerebral involvement observed in 19% of cases was always associated with other sites of infection. Antifungal treatment was empirically administered in 49 patients (83%); 7 patients underwent radical surgical debridement (12%). Therapy was successful for only 18 patients (37%). Forty-seven patients died within 3 months of the diagnosis of fungal infection: the cause of death was mucormycosis in 41 patients (87%) and progression of hematologic disease in 6 patients (13%). At univariate analysis, the factors that correlated with a positive outcome from infection were the following: male sex, amphotericin B treatment, neutrophil recovery from post-chemotherapy aplasia. At multivariate analysis, the only factor that significantly correlated with recovery from infection was the liposomal amphotericin B treatment.

Interpretation and Conclusions. Mucormycosis is a rare filamentous fungal infection that occurs most frequently in neutropenic patients with acute leukemia. It does not seem to have increased in recent years. Although a reduction of mortality has been observed recently, the mortality rate still remains high. Extensive and aggressive diagnostic and therapeutic procedures are essential in order to improve the prognosis in these patients.

Key words: mucormycosis, leukemia, lymphoma.

From the Istituto di Ematologia, Università Cattolica S. Cuore, Roma (LP, LF); Clinica di Ematologia, Università di Ancona (MO, LC); Divisione Talamona, Ospedale Niguarda Cà Granda, Milan (AN); Cattedra di Ematologia, Università di Udine (AC); Cattedra di Ematologia, Università Umberto I, Napoli (MP); Unità di Microbiologia, Divisione di Ematologia, Ospedale Civile Spirito Santo, Pescara (DD); Dipartimento di Biotecnologie Cellulari ed Ematologia, Università «La Sapienza», Roma (CG, PM); Istituto di Clinica Medica 1, Università di Perugia (ADF), Italy

*Correspondence: Dr. Livio Pagano, Istituto di Ematologia Università Cattolica del S.Cuore largo A. Gemelli 8, 00168 Rome, Italy.
E-mail: lpagano@rm.unicatt.it*

Mucormycosis is an invasive fungal infection caused by various members of the class *Phycomycetes*, especially *Mucoraceae*, subdivided into the genera *Absidia*, *Rhizopus* and *Mucor*. After aspergillosis, mucormycosis is the second most common mycosis caused by filamentous fungi. Overall, genera of the order *Mucorales* represent the third leading cause of invasive fungal infections following *Aspergillus* and *Candida* species.[1-5] Among patients with hematologic disorders, mucormycosis most commonly occurs in those with acute leukemia or lymphoma who have developed neutropenia due to malignancy or to chemotherapy, and in transplanted patients receiving immunosuppressive treatment.[2,6-8] Rhino-cerebral, maxillo-facial and pulmonary infections are the most frequent clinical forms, but neutropenic patients are at a high risk of developing a disseminated mucormycosis. In fact dissemination occurs in up to 40% of mucormycosis in patients with hematologic malignancies[2,9,10-12] and all of these manifestations are characterized by a high rate of mortality.[2,13]

We have already analyzed the epidemiological characteristics of mucormycosis in patients with hematologic disorders.[2] This new analysis is an update of the previous study and a re-evaluation of some of its aspects; in fact the recent availability of more effective diagnostic tools and new antifungal drugs, together with a larger series of patients, could provide interesting new considerations. We reviewed the clinical features of 59 patients with a hematologic malignancy who developed mucormycosis in order to evaluate the clinical spectrum of the disease, its diagnosis and its treatment. Factors that may have influenced the outcome of this infectious complication were also considered.

Design and Methods

Eighteen Hematology Departments took part in this study. The clinical records of patients affected by a hematologic malignancy with a diagnosis of mucormycosis in the period between January 1987 and December 2001 were reviewed.

The diagnosis of mucormycosis was made *in vivo* and at autopsy by demonstrating the organism in the tissue of a biopsy specimen, according to previously reported criteria.[2]

The following information was extracted from the clinical records of these patients: demographic characteristics; type and stage of hematologic malignancy; clinical symptoms and signs of infection; radiological findings; site of infection; laboratory findings (e.g. neutrophil count, microbiological isolates); treatments received; cause of death; autopsy findings.

Statistical methods

Definitions and end-points of the study were agreed upon prior to data retrieval from the clinical records. Success was defined as the disappearance of all signs and symptoms of the treated fungal infection or continuous improvement and clinical evolution compatible with responding disease Failure was defined as death attributed to the fungal infection as a primary or contributing cause, or progressive infection while on therapy or within 1 month of last therapy.

Data were analyzed by descriptive statistical methods and differences between groups were calculated using the χ^2 test or Fisher's exact test when appropriate.

Factors affecting infection outcome (death vs no death) were investigated using a stepwise backward method and were also excluded from the model when the probability was higher than 0.1. Results are presented as odds ratios (with the 95% confidence interval). The best cut-off of continuous variables was ascertained empirically using correlation coefficients.

Statistical significance was established at $p < 0.05$ (two sides). Data were analyzed using an SPSS statistical package (SPSS, Chicago, IL, USA).

Results

Clinical and laboratory features of the patients

During the study period (1987-2001) 59 episodes of mucormycosis were documented in patients with hematologic malignancies. These patients' characteristics are summarized in Table 1. The great majority (78%) of patients had acute leukemia: acute myeloid leukemia (AML) in 30 patients (51%) and acute lymphoblastic leukemia (ALL) in 16 patients (27%). Non-Hodgkin's lymphoma (NHL) was the underlying malignancy in 6 patients (10%), myelodysplastic syndrome and hairy cell leukemia in 2 patients each (3%) and multiple myeloma (MM), Hodgkin's disease, and chronic myeloid leukemia in 1 patient each.

Table 1. Demographic and clinical characteristics of patients with mucormycosis.

Patients, n.	59
Age in years: mean (range)	48 (13-80)
Sex: M/F	30/29
Underlying disease: n. (%)	
• Acute myeloid leukemia	30 (51%)
• Acute lymphoblastic leukemia	16 (27%)
• Non Hodgkin's lymphoma	6 (10%)
• Hairy cell leukemia	2 (3%)
• Myelodyspalstic syndromes	2 (3%)
• Multiple myeloma	1 (2%)
• Chronic myeloid leukemia	1 (2%)
• Hodgkin's disease	1 (3%)
Primary site of infection:	
• Lung	38 (64%)
Alone	28
Plus other sites [involving CNS]	10 [7]
• Sinus	12 (20%)
• Systemic	5 (8%)
• Eye	3 (5%)
• Other*	3 (5%)

*CNS: central enrvous system. *Heart: 1 case, Oral cavity: 1 case; Bowel: 1 case.*

All but two patients had been previously treated with aggressive chemotherapy regimens. In particular 5 patients (9%) developed the infection during transplantation procedures (4 autologous and 1 allogeneic bone marrow transplantation). Twenty-nine patients received 6-methyl-prednisolone (median total dose of 500 mg [range 8-5000] over a median time of 22 days, [range 2-180]). In all these cases glucocorticoids were administered for the treatment of the hematologic disease. Only 10 of the patients (17%) had concomitant diabetes mellitus. None of the patients had a history of previous mycotic infection. Five patients (8.5%) developed mucormycosis despite protective isolation in a laminar airflow room.

When the clinical diagnosis of fungal infection was made, 47 patients were neutropenic and, in particular, 43 of them had a neutrophil count below 0.5×10^9/L; the median duration of neutropenia prior to the diagnosis of mucormycosis was 12 days (range 1-60). Thirty-three of these 47 patients (70%) recovered from neutropenia (neutrophil count $>1\times10^9$/L) in a median time of 7 days after the clinical diagnosis of infection (range 4-30) and 18 of them received granulocyte colony-stimulating factor (rhG-CSF).

Diagnosis

According to the criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG), the diagnosis of mucormycosis was proven in 51 patients and probable in 8 patients.[14] The results of the diagnostic procedures are reported in Table 2.

The mucormycosis was diagnosed by visualizing the characteristic hyphae in sections of tissue and/or in materials such as sputum, exudates and scrapings and by growing the fungus in the laboratory.

In vivo diagnosis of mucormycosis was made in only 32 patients (54%). Biopsy specimens were obtained from 22 of these cases. The diagnosis was made on pulmonary tissue collected by a percutaneous or transbronchial pulmonary biopsy in 10 cases and by pulmonary lobectomy in 1 case. *Mucorales* were identified on biopsy obtained from sinus and/or palatal tissues in 9 patients and after ocular enucleation in 2 cases. In 1 patient, *Mucorales* was documented to be present in bronchial fluid by cytological study of the bronchoalveolar lavage (BAL) fluid. In another 9 patients the mycotic agent was only microbiologically identified: in 4 cases in sputum samples, in 2 from BAL and in 3 from nasal smear samples.

An autopsy was carried out on 33 patients and documented the mucormycosis in 31 cases. In 27 patients autopsy was the only positive diagnostic tool. In two patients who died from progression of their hematologic disease, the autopsy was negative as the patient had apparently recovered from fungal infection, previously diagnosed *in vivo* on a sinus tissue biopsy.

In 30 patients (51%) the *Mucorales* species was microbiologically identified while in 29 patients the etiological agent was not typed (Table 3).

In 38 patients (64%) the main site of involvement of mucormycosis was lung, which represented the sole localization in 28 cases, while the other 10 patients also had secondary localizations. These include the central nervous system (CNS) (n=7), paranasal sinus (n=1), intestine (n=1), liver (n=1). Other primary sites of infection were: orbito-sinus-facial in 14 cases (24%), large bowel in 1 case, myocardium in 1 case, blood in 1 case. CNS involvement, observed in 11 patients (19%), was always associated with infection in other sites. It was probably secondary to hematogenous dissemination or extension to the brain from either nasal or paranasal infection. A disseminated disease was observed in 4 cases (7%) (Table 1).

The most frequent physical finding was fever (80% of cases), with a median temperature of 38.8°C at presentation (range 37.8-39.7°C). In patients with pulmonary mucormycosis, the triad of cough, thoracic pain, and dyspnea was the most common set of symptoms; in 3 cases fatal hemoptysis occurred. In three patients presenting with fever without any clinical signs of pulmonary involvement, the diagnosis of mucormycosis was made only at autopsy (Table 4).

Patients who had rhino-cerebral mucormycosis complained of facial pain or headache and most of them showed orbital involvement consisting of orbital cellulites, parests of extraocular muscles, proptosis and chemosis. Five patients had hemiplegia. The only patient with intestinal involvement had abdominal pain and diarrhea.

Radiographic procedures (standard chest and sinus X-rays; lung, CNS and sinus CT scan) were performed in

Table 2. Results of main diagnostic procedures performed depending on sign and symptoms.

Diagnostic procedures	*Performed*	*Suggestive of invasive fungal infection (%)*
Radiological		
Chest		
• Standard X-ray	41	39 (95%)
• CT-scan	21	21 (100%)
Sinus/CNS		
• Standard X-ray	5	2 (40%)
• Cranial CT-scan	19	11 (58%)
Microbiological*		
• BAL	18	4 (22%)
• Sputum	32	5 (16%)
• Nasal smear	29	9 (31%)
Histologic and/or cytological		
Biopsy	26	22 (84%)
• percutaneous or transbronchial on pulmonary tissue	14	10
• lobectomy	1	1
• sinus and/or palatal tissue	9	9
• ocular enucleation	2	2
Cytological examination of BAL	18	6 (33%)
Autopsy	33	31 (94%)

**More than one site infected in the same patient.*

Table 3. Etiological agents in the 59 cases of mucormycosis.

	Cases	*%*
Mucorales spp.	28	48
Mucor spp.	22	37
Rhizopus spp.	6	10
Cunninghammella	2	3
Absidia corymbifera	1	2

Table 4. Signs and symptoms of the patients at diagnosis by site of infection.*

Sign/symptom	*N°*	*%*
Pulmonary localization	38	64
Fever	38	100
Cough	36	92
Dyspnea	28	72
Chest pain	15	38
Hemoptysis	3	8
Orbito-sinus-facial localization	15	25
Facial edema	15	100
Nasal obstruction	12	80
Facial pain	10	67
Rhinorrhea	8	53
Fever	7	46
Proptosis	4	27
Chemosis	3	20
Palate destruction	3	20
Central nervous system involvement	11	19
Fever	8	53
Headache	7	63
Hemiplegia	7	19
Ptosis, diplopia	4	11
Epilepsy	1	5
Gastro-intestinal tract	1	2
Fever	1	
Abdominal pain	1	
Diarrhea	1	
Rectorrhagia	1	
Myocardium	1	2
Fever	1	
Dyspnea	1	
Thoracic pain	1	
Blood	1	2
Fever	1	

**More than one site infected in the same patient*

52 patients (88%) and the result was suggestive of fungal infection in 41 of them (80%). Chest X-rays were abnormal in 39 of 41 patients examined; chest CT scan showed a pattern compatible with fungal infection in 20 of these patients. In 1 case chest CT scan diagnosed a lung infiltrate not identified by standard X-ray (Table 2). Radiography revealed various patterns such as focal consolidation and widespread infiltrates or nodules. Cavitation was observed in 25% of cases.

Cranial CT scan was performed in 19 patients and revealed evidence of sinus involvement associated with opacification in 11 cases; in 8 cases the presence of brain abscesses was revealed.

Treatment

During neutropenia, 47 patients (80%) had received oral antifungal prophylaxis (18 with fluconazole, 15 with itraconazole, 8 with nystatin, 4 with oral amphotericin B and 2 with ketoconazole) for a median time of 18 days (range 5-90). These 47 neutropenic patients became febrile and received empirical treatment with broad-spectrum antibiotics (β lactam plus aminoglycoside with or without a glycopeptide), which was administered for a median of 10 days (1-35).

Antifungal treatment was empirically administered in 49 patients (83%) after a median time of 90 hours of fever unresponsive to broad-spectrum antibiotics.

Thirty-nine patients were treated with intravenous deoxycholate amphotericin B (AmB) (in 12 patients oral azoles were associated) at a median daily dose of 1 mg/kg (total median dose 1000 mg, range 500-1200); 6 patients received fluconazole (3 cases) or itraconazole (3 cases) only.

Liposomal amphotericin B (L-AmB) was administered in 12 patients at a median daily dose of 3 mg/kg (total median dose 5000 mg, range 2100-19000). In 4 cases this drug was the first line treatment while in the remaining 8 cases it was administered after prior treatment with Amb. They switched from AmB to L-AmB because of renal impairment, intolerance to AmB or because the physicians considered the treatment with AmB a failure.

Seven patients underwent radical surgical clearance: eye enucleation in 2 cases, sinus debridements in 4 cases, and lung lobectomy in 1 case.

Outcome

Therapy was successful in 18 patients (37%). Nine of the 39 patients who received only AmB (23%) and 7 of the 12 patients who received L-AmB (58%) responded to therapy. In 2 of the 6 patients treated with azoles (33%), there was an improvement in clinical status.

Forty-seven patients died within 3 months of the diagnosis of fungal infection. Mucormycosis was the cause of death in 41 of them (87%) while 6 patients who responded to antifungal therapy died from progression of their hematologic disease without signs or symptoms of a new relapsed infection.

Statistical results

The factors considered in the univariate analysis are summarized in Table 5; those statistically significantly associated with recovery from infection are shown in bold. The factors which correlated with a positive outcome from infection were male sex (p = 0.033), AmB treatment (p = 0.012), neutrophil recovery from post-chemotherapy aplasia (p = 0.01). However, at multivariate analysis the only factor that was significantly correlated with recovery from infection was L-AmB treatment [RR=0.5 (CI 0.3-0.8; p = 0.0001)].

In order to examine the effect of the introduction of L-AmB into the clinical use, we divided the overall pop-

Table 5. Univariate analysis of factors that influenced recovery from infection.

Prognostic factor Total patients (n=59)	*Patient cured (n = 13)(%)*	*Patient died (n= 46)(%)*	*p value*
Age			
≤ 50 years	8 (25)	24 (75)	ns
>50 years	5 (18)	22 (82)	
Sex			
Male	10 (33)	20 (67)	0.033
Female	3 (10)	26 (90)	
Phase of underlying hematologic treatment			
Induction	8 (20)	31 (80)	ns
Other	5 (25)	15 (75)	
Use of steroids			
Yes	7(24)	22(76)	ns
No	6(20)	24(80)	
Neutropenia			
< 0.5×10^9/L	8 (18)	35 (82)	0.311
≥ 0.5×10^9/L	5(31)	11(69)	
Duration of neutropenia			
≤14 days	9 (14)	28 (76)	0.742
> 14 days	4 (18)	18 (82)	
Neutrophils recovery			
Yes	6 (33)	16 (57)	0.01
No	7 (17)	26 (89)	
Prophylaxis			
No	2 (17)	10 (83)	0.755
Itraconazole	4 (29)	10 (71)	
Other	7 (21)	26 (79)	
Fever			
Yes	11 (23)	36 (77)	1
No	2 (17)	10 (83)	
Sites of primary infection			
Lung	9 (24)	29 (76)	0.754
Other	4 (19)	17 (81)	
Therapy			
AmB + L-AmB	13 (30)	30 (70)	0.01
Other	0	16 (100)	
AmB dosage			
≤18 g	2 (10)	17 (90)	0.189
> 18 g	11 (27)	29 (73)	
Therapy			
L-AmB	7 (64)	4 (36)	0.001
Other	6 (12)	42 (88)	

ulation of patients into two different groups: those in whom the diagnosis of mucormycosis was made between 1987 and 1994 and those diagnosed between 1995 and 2001. We then compared the features of the two groups (Table 6). The most relevant difference that we found was a higher number of patients treated with L-AmB. However, in spite of an apparent improvement of diagnostic procedures and the use of more effective antifungal drugs (i.e. L-AmB), only a slight, not significant reduction of mortality was observed (72% versus 60%).

Discussion

Mucormycosis is a rare filamentous fungal infection which most frequently arises in patients with hematologic malignancies.[5,8,9,11,12,15-18] The main cause of this infections is probably the prolonged and profound neutropenia secondary to the myeloablative treatments used for the underlying hematologic malignancy. In fact, mucormycosis occurs more commonly in patients with acute leukemia (in our series 78%) than in patients with other types of hematologic malignancies, and the infection is characterized by a high rate of mortality (~70%).

In the past, various factors negatively influenced mortality, including the diagnostic difficulties and the incorrect belief that antifungal prophylaxis could be efficacious against these filamentous fungi.

The diagnosis of mucormycosis is not simple and the demonstration of fungal elements from cytologic preparations (i.e. sputum samples, inflammatory fluid aspirates from sinusitis infection, and broncho-alveolar lavage) is complicated by the difficulty in extracting fungal elements from invaded tissues. Fungal elements may be rare in cytological specimens and when present are often fragmented. Additionally, hyphae may be very focal and may appear in only part of a specimen. A delayed diagnosis means that appropriate doses of antifungal treatment are started late, which can have the consequence of increasing the number of failures.

The present survey represents an update of our previous study. The larger number of cases collected, the availability of better laboratory and radiological diagnostic tools and the introduction of new antifungal drugs in the routine treatment of fungal infections (i.e. lipid formulation of AmB) led us to make a new reappraisal of the characteristics and outcome of mucormycosis in patients with a hematologic malignancy. As already demonstrated, oral antimycotic prophylaxis seems unable to prevent mucormycosis.[2] In fact fluconazole and, in some cases, itraconazole should not be used either for prophylaxis or for treating mucormycosis given the lack of both *in vitro* and *in vivo* susceptibility.[19-23]

The main preventive measure against filamentous fungal infections remains the reduction of environmental exposure;[24] in fact in our series only 5 patients among those who developed mucormycosis were admitted in hepa-filtered rooms.

Table 6. Demographic and clinical characteristics of patients with mucormycosis and univariate analysis divided into two study periods.

Parameters	*1987-1994 (39)*	*1995-2001 (20)*	*Total (59)*
Age			
Median (range)	47(19-75)	51 (13-80)	
≤ 50 years (%)	22 (56)	10 (50)	0.841
>50 years (%)	17 (44)	10 (50)	0.423
Sex			
Male	18 (46)	12 (60)	0.232
Female	21 (54)	8 (40)	
Diagnosis			
AML	22 (56)	8 (40)	
ALL	11 (28)	5 (25)	
NHL	2 (5)	4 (20)	
HD	0	1 (5)	0.161
CML	1 (3)	0	
MM	0	1 (5)	
MDS	1 (3)	1 (5)	
HCL	2 (5)	0	
BMT			
No	39 (100)	15 (75)	0.005
Autologous	0	4 (20)	
Allogeneic	0	1 (5)	
Steroids			
Yes	16 (41)	13 (65)	
Median dosage [mg] (range)	1200 (200-5000)	510 (20-4800)	
Median duration (days)	24 (4-66)	15 (2-180)	0.103
No	23 (59)	7 (35)	
Previous neutropenia			
Median duration [day] (range)	12 (3-60)	10.5 (0-30)	0.160
Neutrophils at diagnosis			
$< 0.1\times10^9$/L	26 (67)	8 (40)	0.169
$0.1\text{-}0.49\times10^9$/L	4 (10)	5 (25)	
$0.5\text{-}0.99\times10^9$/L	3 (8)	1 (5)	
$\geq 1\times10^9$/L	6 (15)	6 (30)	
Neutrophil recovery			
Yes	21 (54)	11 (34)	0.933
No	18 (46)	9 (45)	

The treatment of mucormycosis in patients with hematologic malignancies may require several simultaneous approaches including surgery, antifungal therapy, and medical management of the neutropenia.

In general, surgical resection of isolated pulmonary disease greatly improves survival compared to patients who receive antifungal therapy alone.[13,25] There are even notable cases of mucormycosis being cured by surgery alone.[25-28] However, the clinical conditions of neutropenic patients (low platelet count, low performance status), and the presence of multiple mycotic abscesses frequently do not allow a surgical resection. In our experience surgical resection significantly improves the recovery from infection; however, in the present series only 7 patients underwent surgery. It is remarkable that 6 of them recovered from infection and that 4 of these 6 patients received L-Amb as antifungal treatment. It is possible that more widespread use of combined medical-surgical therapy could further reduce mortality, as already stressed by other authors.[6,11]

When surgical intervention is not possible or difficult to perform because of the site of the infection, antifungal therapy alone can be used, but a successful outcome is rare.[18,29-31]

Deoxycholate AmB is the first-line drug of choice for mucormycosis. In our series AmB treatment statistically improved the patients' outcome, even though it may not be effective in all cases, particularly in patients presenting late in the course of their disease and with disseminated disease. The therapeutic activity of AmB is limited by its potentially severe side effects. Impaired renal function often leads to cessation of therapy.[9,19,20] Furthermore it must be taken in account that AmB does not penetrate the blood-brain barrier readily, so it can be ineffective in CNS mucormycosis. The majority of zygomycetes demonstrate resistance to fluconazole, itraconazole and 5-fluorocytosine.[9,19-23] *In vitro* activity of investigational triazoles such as posaconazole, and ravuconazole has been tested. These studies showed that posaconazole was effective *in vitro* against zygomycetes; however its efficacy *in vivo* remains to be determined.[23,32,33]

In vitro studies have demonstrated that pneumocadin[34] and the echinocandins[35] do not inhibit fungal growth. Furthermore recent clinical trials have stated that both echinocandins[36] and voriconazole,[21] two newer antifungal drugs, are ineffective in the treatment of mucormycosis. In this discouraging situation, L-AmB represents the only possible alternative to conventional AmB, without a significantly increased toxicity even if applied at higher dosage (3-5 mg/kg).

In fact, the liposomal formulations enable the drug to deposit in the reticulo-endothelial system including local sites of infection. The drug is released within these sites through the action of lipases from surrounding inflammatory cells. Furthermore L-AmB penetrates the brain parenchyma and results in high drug concentrations in the brain;[37] a similar effect has also been demonstrated for AmB lipid complex.[38]

The characteristics of our study, retrospective and not randomized, do not allow a demonstration of the superior efficacy of L-AmB, with respect to other treatments but the rarity of mucormycosis excludes the possibility of conducting prospective randomized trials with a significant number of patients, particularly those with

hematologic malignancies. However, our collection of data on a large group of patients does allow some interesting considerations. In our series, we observed a significant reduction in mortality from mucormycosis in those patients who received L-AmB, which resulted to be the most relevant factor influencing the mortality associated with recovery from neutropenia. In fact, in multivariate analysis, L-AmB was the only parameter correlated with survival from the infection. In our series a median daily L-AmB dosage of 3 mg/kg resulted efficacious.

The importance of neutropenia as a factor contributing to the development of infection in patients with hematologic malignancies has already been demonstrated,[39] and the recovery of neutrophils plays a main role in the cure of mucormycosis. In our experience the recovery from aplasia is strictly correlated with a lower mortality rate. Various studies of improved recovery from infection by correcting neutropenia either with granulocyte transfusions[40,41] or by enhancing endogenous neutrophil production using growth factors[42-44] have been published. The use of growth factors reconstituting altered host defenses and reducing the duration of neutropenia might increase the recovery from mucormycosis, even though in our statistical evaluation, this therapeutic approach did not result significant, perhaps because of the low number of cases treated with growth factors.

When we stratified patients according to two different time periods (1987-1994 and 1995-2001), some relevant differences were observed. *In vivo* diagnosis seems to be achieved more easily in recent years and the fungal agent is now frequently specified, but the most important difference we found was the slight reduction in the mortality rate, even if not statistically significant.

In conclusion, mucormycosis is a rare filamentous fungal infection, which does not seem to have increased in the last years. Although a slight reduction in mortality has been observed, the mortality rate still remains high. Among the drugs effective against *Mucorales*, L-AmB seems to be more effective than AmB, probably because high daily doses can be used for longer periods with fewer side effects. Recent pharmacokinetic studies demonstrated the safety and tolerance of high doses of L-AmB (since 15 mg/kg/day);[45] this kind of treatment could be the appropriate approach to mucormycosis, in consideration that literature reviews show that the new antifungal drugs (i.e. voriconazole, caspofungin) do not seem to add new ammunition against these dangerous fungal infections, and we are awaiting data from treatment studies using posaconazole to assess the efficacy of this azole agent in zygomycosis.

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