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Risk factors for Early Mortality in Hematological Malignancy Patients with Pulmonary Mucormycosis

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Keywords

Mucormycosis; lymphocytopenia; risk index score

Introduction

Pulmonary infections caused by *Mucorales* have increased in incidence over the last two decades due to an expanding population of severely immunocompromised patients and improved treatment of more common invasive mold infections such as aspergillosis [1-3]. Mucormycosis is a unifying term used to describe infections caused by fungi belonging to the order *Mucorales* [3].

Patients with hematological malignancies, especially those with acute myelogenous leukemia (AML), and those who have undergone hematopoietic stem cell transplantation (HSCT) are among the highest risk patients for pulmonary mucormycosis (PM) [1, 2]. Crude mortality rate for PM typically exceeds 80% [2], although early treatment with lipid amphotericin B formulations and possibly posaconazole significantly improves outcome [4-7].

Although risk factors for development of PM are well known [2], no studies have examined prognostic indicators (assessed at the time of diagnosis) that could help clinicians stratify patients who are at risk for rapid disease progression and early death [8]. To that end, we retrospectively reviewed all cases of PM from 2000-2012 in our institution to examine whether baseline clinical or laboratory risk factors at the time of the diagnosis of PM could serve as prognostic markers for stratifying patients at low versus high risk for early death (within 4-weeks).

Patients and Methods

We analyzed all hematological malignancy patients diagnosed with PM at MD Anderson Cancer Center, Houston, Texas, during a 12-year period from January 1, 2001 to January 1,

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2012. Only patients who met the criteria for proven or probable PM according to the revised definitions of the European Organization for Research and Treatment of Cancer (EORTC) and Mycoses Study Group (MSG) were included in the study [9]. Mold isolates were identified according to standard morphological criteria [10].

Patient electronic records were reviewed for demographic characteristics, type and status of underlying malignancy, history of HSCT, risk factors for invasive mold infection present at diagnosis (e.g., neutropenia, lymphocytopenia, monocytopenia, receipt of adrenal corticosteroids or anti-T cell antibodies, graft versus host disease [GvHD]), metabolic abnormalities (e.g., diabetes, hyperglycemia, acidosis, malnutrition, iron overload), severity of presenting disease based on chest / sinus computed tomography (CT), and initial treatment strategies employed during the first 28 days following the diagnosis of PM. We excluded patients with mixed fungal pulmonary infections.

Neutropenia was defined as a neutrophil count less than $500/\text{mm}^3$, whereas monocytopenia was defined as a monocyte count less than $10\text{ cells}/\text{mm}^3$. Lymphopenia and severe lymphopenia were classified as an absolute lymphocyte count (ALC) less than $500\text{ cells}/\text{mm}^3$ and $100\text{ cells}/\text{mm}^3$, respectively. Malnutrition was defined as a serum albumin level less than 3.5 g/dL . PM was considered to be a breakthrough infection rather than a “de novo” if the infection developed more than 7 days after initiation of preventive or empiric antifungal therapy.

Delayed *Mucorales* - active therapy was defined as the initiation of effective treatment more than 5 days after primary symptoms based on previous studies [7]. The primary endpoint was mortality at 4 weeks after PM diagnosis. Death was attributed to PM if the patient had clinical, microbiological, histological and/or radiological evidence of active fungal infection at the time of death. The study protocol was reviewed and approved by The MD Anderson Institutional Review Board.

Statistical analysis

Univariate analysis, which consisted of chi-square or Fisher's exact test for categorical independent variables and logistic regression for continuous independent variables, were used to identify factors present at the time of initial clinical presentation associated with 28-day crude mortality. A multivariable Cox Proportional Hazards Regression model was built in a forward stepwise fashion using biologically plausible variables identified by univariate analysis ($P < 0.1$) accounting for potential confounders. Continuous variables were analyzed continuously or categorically using cut-off threshold values identified by classification and regression tree (CART) partitioning. Variables retained in the multivariate model were then assigned a weighted score based on the adjusted hazard ratios rounded to the nearest whole number from the regression model, which was then added to the baseline APACHE II score calculated at the time of PM diagnosis. Receiver-operator curves (ROC) were used to analyze the ability of the risk score to differentiate non-survivors from surviving patients at 28-days, and assign a breakpoint score associated with high risk of early death. Antifungal and other treatment variables occurring after diagnosis were not included in the development of the model. Time to death following the initial clinical signs of PM were then compared in patients with low versus high-risk scores using Kaplan-Meier curves, and mortality rates were compared among groups using the log-rank test. All analysis was performed with SPSS version 20 (IBM, Armonck, NY) and Medcalc Software Packages (Ostend, Belgium).

Results

Patient characteristics and risk factors

We identified 75 patients with PM over the 12-year study period (13 proven / 62 probable) (Table 1). The male:female ratio was 2:1 (50 males and 25 female patients). The median age at diagnosis was 57 years (range, 16-76 years). The vast majority of the patients were Caucasians (81%). Thirty patients (40%) had a diagnosis of AML or myelodysplastic syndrome (MDS). Forty three patients (57%) had active hematological malignancy at the time of diagnosis. Moreover, thirty-six patients (48%) were HSCT recipients. Of these, 29 (81%) received allogeneic stem cell transplants and 19 (66%) patients had developed severe GvHD. A history of diabetes mellitus and a serum glucose level higher than 200 mg/dL were present in 23 (31%) and 25 (34%) patients at the time of diagnosis, respectively.

Neutropenia and lymphopenia were present at diagnosis in 43 (57%) and 48 (64%) patients, respectively, whereas monocytopenia was present in 39 (52%) of the study cohort. Among patients with neutropenia, 28 (65%) had an ANC count less than $100/\text{mm}^3$. The median duration of neutropenia before diagnosis was 10 days (range, 1-100 days). Only 18 patients (24%) recovered from neutropenia during the infection course. Additionally, among patients with lymphopenia, 34 (71%) had severe lymphopenia. Although concomitant neutropenia was common in patients with ALC count higher than $500/\text{mm}^3$, it was less common in patients with severe lymphocytopenia as 60%, 32% and 15% of patients with ALC $>500/\text{mm}^3$, $100\text{-}500/\text{mm}^3$ and $< 100/\text{mm}^3$ were neutropenic, respectively. In addition, an ALC count lower than $100/\text{mm}^3$ was common in patients in patients with uncontrolled malignancy (50%) and recipients of allogeneic HSCT (38%) ($P=0.015$).

Clinical Presentation and Diagnosis

The vast majority of the patients (91%) with PM had concurrent sinus *Mucorales* infection, whereas 16% had disseminated disease. PM was radiologically presented with pulmonary nodules in 60 patients (80%); of these 23 patients (31%) had multiple (>10) nodules bilaterally, while 27 patients (36%) had radiographic evidence of a pleural effusion. Overall, PM presented as a breakthrough infection in 56 cases (75%). The most common antifungal regimen preceding breakthrough infection was voriconazole (54%).

Risk Stratification

Several variables were associated by univariate analysis with 28-day crude mortality in patients with PM (Table 1). When these variable were entered stepwise in a forward fashion in a Cox-proportional hazards regression model along with the APACHE II score, only three baseline variables were independently associated with mortality: APACHE II, lymphocyte count at diagnosis, and LDH count at diagnosis. Significant differences in baseline median lymphocyte count ($470\text{ cell}/\text{mm}^3$ vs. $50\text{ cells}/\text{mm}^3$, $P=0.003$) and serum LDH (1027 IU/L vs. 561 IU/L , $P=0.002$) were evident between surviving and non-surviving patients, respectively (Figure 1). These two continuous variables were subjected to CART partitioning to identify cut-offs associated with increased risk of death, which identified breakpoints of a lymphocyte count of $< 100\text{ cell}/\text{mm}^3$ and an LDH $> 655\text{ IU/L}$. Hence, the final regression model used to devise a risk score as follows: (i) baseline APACHE II (HR 1.1, 1.02-1.2, $P=0.01$) 1 score point added per point of APACHE II; (ii) lymphocyte count $< 100\text{ cells}/\text{mm}^3$ (HR 4.0, 1.7-9.4, $P=0.002$) 4 points added if condition was present at diagnosis; and (iii) LDH > 655 (HR 3.7, 1.29-10.23, $P=0.015$) 4 points added if the condition is present at diagnosis. A resulting risk score was then calculated for each patient in the database.

The resulting risk score (median 19, range 8-37) was then calculated for each patient in the study and analyzed by ROC analysis to define the optimal cut-off value associated with 28-crude mortality (Figure 2a). Overall the risk score accurately classified a majority of patients at baseline who died from PM by day 28 with an aROC of 0.87 (0.77-0.93), $P<0.0001$. A risk score > 22 was found to be the optimal cut-off for classifying early patient death, with a sensitivity of 75%, specificity of 87%, positive predictive value of 78% and negative predictive value of 85%. The calculated risk score was superior to APACHE II alone for discriminating non-surviving versus surviving patients at 28 days after diagnosis (aROC 0.88 versus 0.81, respectively, $P=0.02$).

Comparison of Kaplan-Meier curves of PM patients with risk scores of > 22 ($n=27$) versus ≤ 22 ($n=48$) confirmed a significantly higher rate of mortality within 28-days of initial PM presentation (HR 8.2, 3.6-18.9, $P<0.0001$) and higher cumulative 28-day mortality (14.6% vs. 78%, $P<0.001$). The estimated median survival time in PM patients with a risk score > 22 was 7 days.

Antifungal Treatment

The majority of patients (47 [73%]) received *Mucorales* - active antifungal therapy, either amphotericin B formulation (54 [72%]) (as monotherapy or in combination with other antifungal regimens) or posaconazole (10 [13%]) (as monotherapy or in combination with other antifungal regimens) within 5 days after symptoms initiation. Administration of appropriate therapy (over 5 days) was delayed in 28 patients (37%). Immune augmentation therapy included white blood cell (WBC) transfusions, and administration of hematopoietic growth factors (granulocyte-macrophage colony-stimulating factor / granulocyte colony-stimulating factor) or interferon- γ . Thirty-one percent of the patients received a colony-stimulating factor during treatment, 8% WBC transfusions and 7% interferon- γ . Surgical management, including debridement and wedge resection, was performed in 28 patients (37%). Overall, 28 of 75 patients (37%) died within 4-week follow up (median time of death, 34 days after diagnosis [range, 0-94 days]). No treatment variables were found to be independently associated with improved survival when patients were stratified by the mortality risk score.

Discussion

Mucormycosis has emerged as the second most common invasive mold infection after aspergillosis in patients with hematological malignancies and allogeneic HSCT [2]. In this 12-year retrospective study, we identified 75 such patients with PM. The most important conditions predisposing to mucormycosis, according to various studies, include malignant hematological diseases with or without HSCT, prolonged and severe neutropenia, poorly controlled diabetes mellitus with or without diabetic ketoacidosis, iron overload, major trauma, prolonged use of corticosteroids, illicit intravenous drug use, neonatal prematurity and malnourishment [3, 11, 12]. Not surprisingly, 57% and 64% of our patients, respectively, were profoundly neutropenic and lymphocytopenic. Prior corticosteroid therapy (55%) and diabetes mellitus (31%) appeared to be common additional risk factors for PM. Moreover, 57% of the patients had refractory hematologic disease and thus received intensive cytotoxic chemotherapy. Also, 48% of the patients underwent HSCT, 81% of whom were allogeneic transplant recipients.

We stratified our patient population according to the probability of death using easily available clinical, laboratory and radiological variables at the time of diagnosis. Although historically invasive mucormycosis has been associated with severe morbidity and mortality in most patients with hematological malignancies [11], in the present study, many patients (63%) had a favourable 4-week outcome which is in agreement with recent studies that have

also shown a significant decline in both early (6-week) and late (12-week) mortality in these patients [13, 14]. Similar studies in patients with hematological malignancies and HSCT [15-18] or solid organ transplantation [19, 20] with invasive aspergillosis have demonstrated several prognostic risk factors of mortality, which may assist in the development of treatment intensity algorithms and clinical trials.

In our univariate analysis twelve such variables were found to be significantly different between 4-week survivors and non survivors; male sex, total bilirubin, thrombocytopenia, LDH, creatinine clearance, acidosis, GvHD, active malignancy, severe neutropenia, lymphocytopenia, monocytopenia and voriconazole breakthrough infection. Nevertheless, multivariate analysis accounting for severity of underlying disease revealed only baseline severe lymphocytopenia and a high LDH serum level (> 655 mg/dL) as independent predictors of early death. Consequently, we identified two different prognostic groups using these variables: patients with a 28-day crude mortality rate of $< 15\%$ (score ≤ 22) and patients with a mortality rate of 75% (score > 22).

The outcome of mucormycosis depends on several factors, including the site of infection, the immune status of the host and the use of surgery or other adjunctive treatments [21, 22]. Chamilos et al. reported that the initiation of polyene therapy within 5 days after diagnosis of mucormycosis was associated with improvement in survival, compared with initiation of polyene therapy at ≥ 6 days after diagnosis (83% vs.49% survival) [7]. In the same study active malignancy ($P=0.003$) and monocytopenia ($P=0.01$) at the time of diagnosis of infection were also independently associated with a poor outcome, whereas salvage posaconazole-based therapy ($P=0.01$) and neutrophil recovery ($P=0.009$) were predictive of a favorable outcome [7]. However, this analysis included patients prior to 2000 when diagnosis and treatment outcomes were considerably worse than the current era. Likewise, previous investigators have emphasized the important role of early neutrophil recovery and treatment with high dose amphotericin B [23-25]. Of interest, a recent prospective study on 20 patients with mucormycosis (with pulmonary and non-pulmonary sites of infection) showed that active malignancy ($P=0.03$), neutropenia ($P=0.03$), and iron overload ($P=0.03$) were significantly associated with 90-day mortality in univariate analysis, whereas no association was found with amphotericin B dose or the use of other antifungal therapy (i.e. echinocandin, posaconazole) [8].

Nevertheless, in the current study only lymphocytopenia and high LDH levels, which probably reflects activity of the underlying malignant disease, were significant risk factors for poor outcome when analysis was adjusted for underlying severity of illness (APACHE II). Recent studies have shown the significance of lymphocytes on immunity against *Mucorales*. Specifically Schmidt et al. have demonstrated *Mucorales* specific T cell are present in healthy volunteers and patients with mucormycosis [26], while Potenza et al. suggested that T-cell immunotherapy could be an appealing future therapeutic strategy in these patients [27]. Interestingly, neutropenia was rare among severely-lymphocytopenic patients (only 15% of patients with ALC < 100 were neutropenic).

It was rather difficult to identify the true impact of first line antifungal regimens on survival, due to the plethora of regimens, treatment alterations, and combinations of antifungal agents that utilized during the management of infection. Nevertheless, no benefit was detected for combination therapy in either low or high risk patients. Of note, as randomized, placebo-controlled phase III clinical trials comparing combination therapy versus monotherapy in patients with PM are lacking [4, 28, 29], clinicians continue to confront the dilemma of whether/ and when they should administer combination treatment. Thus, stratification of patients into different risk groups based on an index score system might lead to both avoidance of combination overtreatment and reduction of drug-induced toxicity and cost.

Undoubtedly, our study had several limitations, as it was a retrospective single-institution study that described the risk factors of mortality in patients with PM over a decade. Furthermore, one need to be cautious on the exact significance of lymphocytopenia means in our experience as we provide no information about T-cell subsets (CD4/CD8 lymphocytes), B cells, NK cells. Thus, multi-center clinical trials are needed for prospective validation of the risk index scores in order to develop and validate robust prognostic scores for rare infections such as PM. Future studies of mucormycosis should also probably include baseline ALC as a prognostic marker of immunosuppression severity in hematological malignancy patients. The prospective trials evaluating more aggressive therapeutic interventions (i.e. combinations or high doses of liposomal AMB in first line treatment regimens) should be reserved in priority for these patients.

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Figure 1.

Median baseline lymphocyte count and serum lactate dehydrogenase at diagnosis in survivors versus non-survivors with pulmonary mucormycosis

Baseline lymphocyte count (a) and serum LDH (b) at time of initial clinical presentation. Central box represents values from the 25th percentile to the 75% percentile. The middle line represents the median. The vertical whiskers represent minimum and maximum values. Dots outside the whiskers are larger than the upper quartile plus 1.5x the interquartile range (inner fences). Triangles represent values larger than the upper quartile plus 3x the interquartile range (outer fences). In the lymphocyte concentration analysis, the triangle symbols were observed in patients with uncontrolled lymphocytic malignancies (chronic lymphocytic leukemia n=2, Burkitt's lymphoma n=1). Groups were compared by Mann-Whitney U.

Figure 2.

Predictive score performance and cumulative survival in patients with pulmonary mucormycosis

(a) Area under the Receiver-operator curve (aROC) analysis of calculated risk score and classification of patient 28-crude day mortality. (b) Kaplan-Meier Analysis of PM patients with calculated risk scores ≤ 22 versus > 22. HR 8.2, 3.6-18.9, $P<0.0001$.

Table 1

Demographic and disease characteristics at time of diagnosis in patients with pulmonary mucormycosis (2000-2012).

Characteristic	Survivors at 4 weeks (n=47)	Non-Survivors at 4 weeks (n=28)	P value ^a
Male sex	35 (81)	15 (54)	0.06
Age (range, years)	53 (22-76)	51 (16-75)	0.70
Race			0.89
Caucasian	38 (81)	23 (82)	
Hispanic	3 (6)	2 (7)	
African American	5 (11)	3 (11)	
Asian	1 (2)	0 (0)	
Body mass index (range)	25 (17-39)	27 (16-36)	0.27
Total bilirubin (range, mg/dL)	1.1 (0.5-10)	2.7 (0.5-25)	0.09
Platelets (range, $\times 10^9/L$)	27 (5-70)	35 (8-95)	0.07
LDH (range, IU/L)	806 (32-4684)	1813 (413-8378)	0.002
Albumin (range, mg/dL)	2.6 (1-4)	2.4 (1-4)	0.56
Ferritin (range, ng/mL)	3018 (347-7592)	2148 (331-5070)	0.64
Estimated creatinine clearance (range, ml/min)	43 (10-99)	54 (10-98)	0.05
APACHE II	14 (7-30)	20 (9-31)	<0.001
CMV antigen positive	7 (15)	4 (14)	0.61
AML/MDS	19 (40)	11 (39)	0.56
Active malignancy	23 (49)	20 (71)	0.05
HIV	1 (2)	1 (4)	0.61
History of diabetes mellitus	14 (30)	9 (32)	0.56
Hyperglycemia (>200 mg/dL)	11 (23)	14 (50)	0.28
Acidosis	2 (4)	9 (32)	0.002
Allogeneic HSCT	21 (47)	8 (29)	0.13
MMR or MUR donor	10 (21)	5 (18)	0.48
Myeloablative conditioning	7 (15)	5 (18)	0.20
Severe GvHD (stage III-IV)	15 (32)	4 (14)	0.08
Neutropenia (< 500 cells/mm ³)	16 (34)	12 (43)	0.006
Severe lymphopenia (< 100 cells/mm ³)	14 (30)	20 (71)	< 0.001
Monocytopenia (< 10 cells/mm ³)	17 (36)	19 (68)	0.08
Anti-T cell monoclonal Abs	5 (11)	2 (7)	0.41
Breakthrough infection	35 (74)	21 (75)	0.59
Voriconazole breakthrough infection	22 (47)	18 (64)	0.11
Cultured Mucorales species			0.33
Mucor	7 (15)	6 (21)	
Cunninghamella	6 (13)	2 (7)	
Rhizopus	16 (34)	13 (46)	
Other	9 (19)	1 (4)	
Site of infection			

Characteristic	Survivors at 4 weeks (n=47)	Non-Survivors at 4 weeks (n=28)	P value ^a
Disseminated disease	9 (19)	3 (11)	0.27
Sinopulmonary	41 (X)	27 (96)	0.27
Other	2 (4)	1 (4)	0.68
CT nodules			0.88
None	9 (19)	6 (21)	
<5	9 (19)	3 (11)	
5-10	4 (9)	3 (11)	
>10	16 (34)	7 (25)	
Pleural effusion	17 (36)	10 (36)	
Day of treatment initiation (range)	3.3 (0-8)	3.4 (1-7)	0.34
Treatment delay > 5 days	15 (32)	13 (46)	0.35

^c Available in 64 patients

^d Anti-thymocyte globulin or alemtuzumab.

Abbreviations: LDH, lactate dehydrogenase; CMV, cytomegalovirus; MDS, myelodysplastic syndrome; AML, acute myelogenous leukemia; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; MMR, mismatched related; MUR, matched unrelated; GvHD, graft-versus-host disease; Abs, antibodies; CT, computed tomography.