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Original article

Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis

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ABSTRACT

In view of the poor outcomes associated with mucormycosis in patients with haematologic malignancies (HM) and haematopoietic cell transplant recipients, antifungal combinations are frequently used, yet the value of such strategy remains unclear. We reviewed the records of HM patients treated for mucormycosis from 1994 to 2014. The primary outcome was 6-week mortality after treatment initiation. Of the 106 patients identified, 44% received monotherapy and 56% received combination treatment as initial therapy. Six-week mortality was associated with disseminated mucormycosis (p 0.018), active malignancy (p <0.01), higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores (p <0.001), neutropenia (p 0.049), lymphopenia (p 0.0003) and intensive care unit (ICU) admission at diagnosis (p 0.0001). Survivors were more likely to have localized mucormycosis (p <0.01) and to receive hyperbaric oxygen therapy (p 0.02). There were no differences in mortality between monotherapy and combination treatment groups (43% vs. 41%; p 0.85). In multivariate analysis, lymphopenia (odds ratio (OR), 5.5; 95% confidence interval (CI), 1.9–15.9; p 0.002) and ICU admission at diagnosis (OR, 8.2; 95% CI, 2.3–29.2; p 0.001) were associated with increased mortality. Localized mucormycosis was associated with better outcome (OR, 0.06; 95% CI, 0.01–0.6; p 0.019). Initial combination treatment had no impact on mortality, even after propensity score adjustment (OR, 0.8; 95% CI, 0.3–2.4; p 0.69). A weighted mortality risk score was then calculated for each patient based on the factors independently associated with mortality and baseline APACHE II score. In the low-risk group ($n = 49$), 13% of monotherapy versus 15% of combination therapy patients died within 6 weeks (p >0.99). In the high-risk group ($n = 57$), 71% of monotherapy versus 61% of combination therapy patients died within 6 weeks (p 0.42). With the current status of mucormycosis diagnosis, there was no difference in mortality in HM patients, whether they received monotherapy or combination treatment as initial therapy. Earlier diagnosis and immune reconstitution are unmet needs to affect outcomes. **A. Kyvernitakis, CMI 2016;22:811.e1–811.e8**

Introduction

Once considered an uncommon infection, mucormycosis has emerged as the second most common invasive mould infection after aspergillosis for patients with haematologic malignancies (HM) and haematopoietic cell transplant (HCT) recipients [1–3]. Mucormycosis is a life-threatening opportunistic infection caused by fungi of the order Mucorales, previously classified under the order Zygomycetes [4]. As HCT becomes a more broadly available option, and as the population of immunocompromised patients with HM increases, the number of patients affected by this infection will continue to rise [5].

Mucormycosis typically presents as sinopulmonary, rhinocerebral, cutaneous or disseminated disease. In immunocompromised hosts, sinopulmonary involvement is the dominant clinical

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presentation, which is associated with mortality rates as high as 80% in heavily immunosuppressed hosts [1]. Successful treatment largely depends on timely diagnosis, control of the underlying condition and broad surgical debridement, in conjunction with systemic Mucorales-active antifungal therapy [6,7]. Currently the only antifungals with proven activity against Mucorales are amphotericin B (mainly the lipid formulations), posaconazole and the newly approved triazole isavuconazole [6,8–11]. In addition, *in vivo* animal models and limited retrospective clinical data suggest a survival benefit from combining liposomal amphotericin B (LAMB) with either echinocandins or posaconazole [10,12–14].

In view of the high mortality associated with this infection, clinicians often elect to administer combination treatment. However, there is no proven benefit with this therapeutic approach, and only a randomized prospective clinical trial can accurately answer this question. However, because of the rarity of infection, the heterogeneity of the affected population and the continuous advancements in systemic antifungal therapy, conducting such a study is not feasible practically. Thus, and despite the limitations, we conducted a retrospective study since the availability of LAMB to evaluate the outcomes of patients with HM and mucormycosis when treated with monotherapy or combination of antifungals as initial therapy. In an effort to address potential confounders, we calculated the propensity to receive single-agent or combination antifungal therapy as an initial regimen, given the patients' pre-treatment characteristics.

Materials and Methods

Study design

We retrospectively reviewed the microbiology databases and medical records of patients treated for mucormycosis at he University of Texas MD Anderson Cancer Center between January 1994 and October 2014. This study was approved from the institutional review board.

Patients were eligible for inclusion if they met the European Organization for Research and Treatment of Cancer/National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group definition for invasive mucormycosis infection [15]. Patients were excluded if they were younger than 18 years old, had solid tumours, had possible mucormycosis, had a mixed fungal infection or died within 3 days of treatment initiation.

Definitions

Site of infection was categorized as localized (soft tissue involvement or isolated infection not involving the respiratory tract), sinopulmonary or disseminated (infection with two or more noncontiguous sites of involvement). Breakthrough infection was defined as an infection that occurred in the setting of a patient receiving antifungal prophylaxis for $\geq$3 consecutive days in the previous 2 weeks before the diagnosis of mucormycosis.

Neutropenia was defined as a neutrophil count of $\leq$500 cells/μL, lymphocytopenia as a lymphocyte count of $\leq$500 cells/μL and monocytopenia as a monocyte count of $\leq$10 cells/μL, all at the time of diagnosis. Neutrophil recovery was defined as a sustained neutrophil count of $\geq$500 cells/μL for 3 consecutive days after the diagnosis of neutropenia. Malnutrition was defined as a serum albumin level of $\leq$3 g/dL at the time of diagnosis. Corticosteroid use was considered significant if a patient had received $\geq$600 mg of prednisone equivalent dose within 1 month before treatment initiation for mucormycosis.

Initial treatment was defined as any Mucorales-active antifungal agent (i.e. LAMB or posaconazole, alone or in combination with echinocandins) started within the first 7 days from baseline. Patients were separated into two groups according to the different modalities of initial treatment (monotherapy or combination treatment). Monotherapy was defined as single-agent treatment with LAMB or posaconazole. Combination therapy was defined as any combination of LAMB, posaconazole and echinocandins provided as initial treatment.

Because our study spanned two decades, we had to consider the time effect. Posaconazole was introduced and started being used after 2004, so we divided the cohort in two groups on the basis of the time of diagnosis: 1994–2004 and 2005–2014.

Statistical analysis

The primary outcome of the study was early survival, defined at 6 weeks after treatment initiation. Day of treatment initiation was defined as day 0. A secondary analysis using 12-week mortality as an outcome was performed (Supplementary Material).

Categorical variables were compared by the chi-square or Fisher exact test, as appropriate. Continuous variables were compared by the Wilcoxon rank-sum test. Logistic regression analysis was used to identify factors that were independently associated with mortality. The propensity score for receiving combination therapy was computed on the basis of a logistic regression model with the treatment approach as the dependent variable. This model included baseline characteristic variables that had a $p \leq 0.2$ in the univariate analysis.

For the analysis of the association between type of therapy and mortality, we first chose covariate adjustment for the propensity score analysis due to the sample size limitation. A logistic regression analysis with propensity score adjustment was performed. In this model, type of therapy, propensity score for receiving combination treatment, and all factors that were independently associated with mortality were included. This aimed to evaluate the association between type of therapy and mortality in multivariate analysis while adjusting for baseline imbalances. Another propensity score analysis using inverse probability of treatment weighting to adjust for bias was performed. Propensity score–adjusted survival curves were estimated separately for patients who received different treatment approaches using a Cox proportional hazards model. In addition, mortality risk-stratified analysis of the association between therapy type and mortality was performed. A weighted mortality risk score was calculated for each patient on the basis of the factors independently associated with mortality and baseline Acute Physiology and Chronic Health Evaluation (APACHE) II score [16]. Patients were divided into two groups: low and high risk for mortality based on the optimal cutoff risk score determined by receiver operating curve (ROC) analysis. Within each group, mortality rates were compared between patients with different therapy approaches. Kaplan-Meier survival curves were estimated separately for patients with different treatment approaches at different risks for mortality, and survival probabilities were compared among them by the log-rank test. All tests were two-sided with a significance level of 0.05. Data analyses were performed by SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

We identified 106 HM patients with mucormycosis. Of them, 74 (70%) had proven and 32 (30%) probable infection. The majority had underlying leukaemia (87%), had currently active malignancy (65%) and had previously undergone HCT (51%). Among the HCT recipients, 82% had history of graft-versus-host disease (GVHD), and