

## INVASIVE FILAMENTOUS FUNGAL INFECTIONS IN HEMATOPOIETIC TRANSPLANT RECIPIENTS AFTER RECOVERY FROM NEUTROPENIA.

\*Shaukat A<sup>1</sup>, Bakri F<sup>1</sup>, Young P<sup>1</sup>, McCarthy, Jr. PL<sup>1</sup>, Hahn T<sup>1</sup>, Loud P<sup>1</sup>, Cheney RT<sup>1</sup>, Walsh TJ<sup>2</sup>, Segal BH<sup>1</sup>

<sup>1</sup>Roswell Park Cancer Institute, Buffalo, NY and <sup>2</sup>Pediatric Oncology Branch, NCI, NIH, Bethesda, MD

Invasive filamentous fungal infections (IFFI) are important causes of morbidity and mortality in highly immunocompromised patients with cancer. In allogeneic bone marrow and stem cell transplant (BM/SCT) recipients, IFFI occurs as a consequence of neutropenia following the conditioning regimen, and, with increasing frequency, following myeloid engraftment in the setting of potent immunosuppressive regimens used to treat graft versus host disease (GVHD). Our objectives in this study were to conduct a retrospective analysis of the clinical, radiologic and histopathologic manifestations and outcome of IFFI diagnosed in BM/SCT recipients at Roswell Park Cancer Institute, Buffalo, NY. Twenty-four BM/SCT recipients with a positive mould culture were identified from the microbiology database. Proven IFFI required recovery of mould from a normally sterile site or histologic documentation of invasive disease. Probable IFFI was only applied to the sinopulmonary tract and required a positive culture of a mould plus compatible radiographic findings in the absence of histopathologic documentation of invasive disease. Based on these criteria, 22 patients were included in the analysis. IFFI was documented after engraftment in 21 (95%) patients. Nineteen (86%) patients were allogeneic BM/SCT recipients. All patients had an underlying hematologic disease, the most common being acute leukemia (n=9; 41%), chronic myelogenous leukemia (n=6; 27%), and non-Hodgkin's lymphoma (n=5; 23%). An *Aspergillus* species was identified in 17 (77%) cases. *Zygomycete* sp. were identified in 4 (18%) patients; in 3 of these cases, mixed infection was documented with an *Aspergillus* sp.. More than one filamentous fungal pathogen was identified in 6 (27%) cases. The predominant site of infection was the lungs alone in 12 (55%). Disseminated infection occurred in 7 (31%). The median time to diagnosis of IFFI was 142 days after transplant (range: 1-28 months). Patients with a related donor were diagnosed with IFFI later than those with unrelated donors (p = 0.001). This finding coincided with a trend toward a higher dose of corticosteroids being administered in the first month of transplant to patients who were diagnosed with IFFI before day 142 versus after day 142 (median methylprednisolone dose of 77 mg/d vs. 50 mg/d, respectively; p=0.07). Duration of neutropenia following the conditioning regimen ranged from 8 to 39 days and did not affect either the time to diagnosis of IFFI or outcome. GVHD was documented in 18 (81%) cases. All patients received either cyclosporine or tacrolimus within 1 month of diagnosis of IFFI. All patients received systemic corticosteroids within 1 month of IFFI diagnosis, with the mean dose ranging between the equivalent of methylprednisolone 10 mg/d to 590 mg/d. Six (27%) patients received OKT3 within 1 month of IFFI diagnosis, principally for the treatment of corticosteroid-refractory GVHD. Three (14%) patients had concurrent cytomegalovirus disease. Twenty (91%) patients received antifungal prophylaxis within 1 month of IFFI diagnosis, consisting of conventional amphotericin B (14%), lipid formulation of amphotericin B (9%), fluconazole (18%), itraconazole capsules (36%; monitoring of serum levels was not routinely done), or >1 antifungal agent (14%). Dyspnea occurred in 14 (64%) patients within 24 hours of IFFI diagnosis. Fever (32%), cough (23%), and chest pain (14%) occurred less frequently. Hemoptysis was not observed. The typical radiologic appearance was similar to findings usually observed in IFFI during neutropenia. Chest CT scans showed patchy infiltrates, single and multiple nodular lesions, and cavitation. Histopathologic material from biopsy or autopsy was available in 15 (68%) patients. The inflammatory exudate consisted of neutrophils, histiocytes, or a mixed cellular response. In some cases, microangioinvasion and coagulative necrosis occurred. Lipid formulations of amphotericin B and conventional amphotericin B were the most common antifungal agents used as therapy following diagnosis of IFFI (45% and 32%, respectively). Only 2 (9%) patients had long-term survival. Four (18%) patients were diagnosed at autopsy. Of the remaining 16 cases, the median survival was 1.7 months after diagnosis of IFFI. Factors associated with mortality within 6 months of diagnosis of IFFI were higher doses of corticosteroids one month prior to infection (p = 0.03), having received OKT3 within one month prior to infection (p = 0.03), and serum creatinine >2 mg/dl at the time of diagnosis of infection (p = 0.01). Survival at 6 months after diagnosis of IFFI was not affected by presence of GVHD, type of transplant, underlying hematologic disorder, baseline Karnofsky performance status, related donor, dose of corticosteroids in the first month after engraftment, or antifungal agent used once fungal infection was identified. Our study shows that IFFI is more common after engraftment than during neutropenia in BM/SCT recipients. Mortality within 6 months of diagnosis of IFFI was significantly more common in patients receiving more potent immunosuppressive regimens for GVHD. The low frequency of typical signs and symptoms and their lack of association with severity of infection or outcome emphasize the importance of having a low threshold for early diagnostic imaging in these patients and underscores the need for improved nonculture-based early detection methods.