The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Original article

Diagnostic-driven antifungal therapy in neutropenic patients using the D-index and serial serum galactomannan testing☆

*Marcia Garnica, Aline Sinhorelo, Laura Madeira, Rodrigo Portugal, Marcio Nucci**

Universidade Federal do Rio de Janeiro (UFRJ), Hospital Universitário, Departmento de Medicina Interna, Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:
Received 7 December 2015
Accepted 5 April 2016
Available online 6 June 2016

Keywords:
Fungal disease
Leukemia
Risk stratification
Neutropenia

ABSTRACT

Introduction: Invasive mold disease is an important complication of patients with hematologic malignancies, and is associated with high mortality. A diagnostic-driven approach has been an alternative to the classical empiric antifungal therapy. In the present study we tested an algorithm that incorporated risk stratification using the D-index, serial serum galactomannan and computed tomographic-scan to guide the decision to start antifungal therapy in neutropenic patients.

Patients and methods: Between May 2010 and August 2012, patients with acute leukemia in induction remission were prospectively monitored from day 1 of chemotherapy until discharge or death with the D-index and galactomannan. Patients were stratified in low, intermediate and high risk according to the D-index and an extensive workup for invasive mold disease was performed in case of positive galactomannan (≥0.5), persistent fever, or the appearance of clinical manifestations suggestive of invasive mold disease.

Results: Among 29 patients, 6 (21%), 11 (38%), and 12 (41%) were classified as high, intermediate, and low risk, respectively. Workup for invasive mold disease was undertaken in 67%, 73% and 58% ($p = 0.77$) of patients in each risk category, respectively, and antifungal therapy was given to 67%, 54.5%, and 17% ($p = 0.07$). Proven or probable invasive mold disease was diagnosed in 67%, 45.5%, and in none ($p = 0.007$) of high, intermediate, and low risk patients, respectively. All patients survived.

Conclusion: A risk stratification using D-index was a useful instrument to be incorporated in invasive mold disease diagnostic approach, resulting in a more comprehensive antifungal treatment strategy, and to guide an earlier start of treatment in afebrile patients under very high risk.

☆ Register number in ClinicalTrials.gov: NCT00982540.

* *Corresponding author.*
E-mail address: mnucci@hucff.ufrj.br (M. Nucci).

http://dx.doi.org/10.1016/j.bjid.2016.04.007

Introduction

Invasive mold disease (IMD) is an important complication of patients with hematologic malignancies, and is associated with high mortality.[1,2] Strategies to reduce the incidence and morbidity associated with IMD include the use of antifungal prophylaxis and empiric antifungal therapy.[3,4] The latter is considered standard of care in patients with persistent or recurrent fever and neutropenia, but since fever is a non-specific manifestation and may have other etiologies (including uncontrolled occult bacterial infection, viral infection and drug fever),[4] a significant number of patients receive antifungal therapy unnecessarily. A diagnostic-driven approach has been studied as an alternative to the empiric therapy. In this strategy, other parameters such as serial serum *Aspergillus* galactomannan antigen (s-GMI) and computed tomography (CT) of the chest and sinuses are used to trigger the initiation of antifungal therapy.[5–7] A major risk factor for IMD in hematologic patients is severe (<100/mm^3) neutropenia lasting >10–15 days,[8–10] and clinicians rely on a certain duration of neutropenia above which an IMD is suspected. A major limitation of this strategy is the lack of a parameter that measures both the intensity and the duration of neutropenia. We developed an index (D-index) that combines the intensity and duration of neutropenia, calculating the area over the neutrophil curve. The index was tested retrospectively in patients with acute myeloid leukemia (AML), and showed a good discriminatory performance in identifying patients with IMD. A cut-off was derived, and showed good sensitivity, specificity, and a very high negative predictive value (97–99%).[11] The high negative predictive value of this index is very similar to that obtained with s-GMI and 1,3-β-D-glucan (BDG) in febrile neutropenic patients.[12,13]

In the present study we tested an algorithm that incorporated the D-index, serial s-GMI and chest, and sinuses CT in high-risk neutropenic patients. We aimed to define a risk stratification parameter to guide a comprehensive diagnostic approach, helping the decision to start antifungal therapy in high-risk neutropenic patients.

Patients and methods

The study was conducted at the Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, Brazil, a tertiary care hospital with ~400 beds, including a hematology and hematopoietic cell transplant (HCT) unit with eight single-bed rooms with high efficiency particulate air (HEPA) filter and positive pressure, and five double-bed rooms without HEPA filter. The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The institution's Ethical Committee ("Comitê de Ética em Pesquisa do Hospital Universitário Clementino Fraga Filho") approved the study (171/09). The study was registered in ClinicalTrials.gov (NCT00982540).

Between May 2010 and August 2012, all adult patients (age ≥18 years) with AML, acute lymphoid leukemia (ALL) or myelodysplasia (MDS) undergoing induction remission chemotherapy who signed an informed consent were included in the study. We excluded patients with a past history of or an active IMD. Patients were treated in rooms with HEPA filters and received standard care for neutropenia, consisting of antibacterial (ciprofloxacin) and antifungal prophylaxis (usually fluconazole). In case of fever (>38 °C), blood cultures were obtained and empiric antibiotic therapy with a β-lactam was started. Blood cultures were repeated in case of persistent or recurrent fever, or as clinically indicated. Modifications in the empirical antibiotic regimen were performed according to the results of cultures and the clinical course of the patient.

Patients were monitored from day 1 of chemotherapy until discharge or death with the D-index and s-GMI performed three times per week (Platelia *Aspergillus* Ag Kit, Bio-Rad, Marnes-la-Coquette, France). The D-index was calculated using the results of absolute neutrophil counts (ANC) performed three times per week, as previously described.[11] Briefly, the calculation of the D-index is based on a graph plotting the ANC during the course of neutropenia, and is the area over the neutrophil curve. Clinically it represents the deficit of neutrophils during the episode.

A workup for IMD (chest and sinus CT scan) was triggered in the following situations: persistent (after six days of antibiotics) or recurrent fever, clinical manifestations of IMD (sinuses, pneumonia, skin nodules), or positive s-GMI (≥0.5). Other tests, including bronchoalveolar lavage and biopsy of skin lesions were performed if clinically indicated. The IMDs were classified as proven, probable, or possible, as previously defined.[14,15]

Assuming the cut-off value of 5800 from the original publication[11] (negative predictive value of 97%) and 3000 (no documentation of IMD below this value in the retrospective study), we stratified patients in three risk categories based on the cumulative D-index: low (<3000), intermediate (3000–5800), and high (>5800) (Table 1). Patients stratified as high risk and either one positive s-GMI, any image on CT scan or any clinical signs or symptom suspicious of an IMD received systemic antifungal therapy (preferably caspofungin, at the dose of 70 mg on day 1 and 50 mg on subsequent days, intravenously). Patients in the low risk group received systemic antifungal therapy only in the presence of typical image of IMD on CT scan (well-circumscribed pulmonary infiltrates, air crescent or cavitary lesions) plus two consecutive positive s-GMI, or upon documentation of proven IMD.[14] Patients in the intermediate risk group received systemic antifungal therapy in the presence of at least two consecutive positive s-GMI tests plus any image in CT scan, one positive s-GMI in the presence of typical images (well-circumscribed infiltrates, air crescent or cavity) or upon documentation of proven IMD. In case of start of antifungal treatment, the duration of therapy was defined by the attending physician on a case by case basis. Of note, since D-index is a dynamic parameter, patients formerly in the low or intermediate risk were classified as high risk group once the cumulative D-index was >5800.

The outcomes of each initial risk group (low, moderate, and high) were compared regarding the incidence of proved and probable IMD, receipt of systemic antifungal therapy and death. Fever was defined as an axillary temperature ≥38 °C.

All data were collected in a case report form and analyzed in the HUCFF. Descriptive data were expressed in percentages and medians, with ranges. Dichotomous variables were