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Title: 'Breakthrough invasive fungal disease in patients receiving posaconazole primary prophylaxis: a four year study'

Abstract

Posaconazole (PSC) is currently recommended as primary prophylaxis in neutropenic patients with acute myeloid leukemia (AML) and in allogenic hematopoietic stem cell transplantation (AHSCT) recipients with graft-versus-host-disease (GVHD). Studies focusing on breakthrough invasive fungal disease (IFD) upon PSC prophylaxis show disparate results. In order to evaluate IFD incidence in patients on PSC prophylaxis and identify IFD risk factors, we carried out a retrospective study of all consecutive patients on PP from 01/2007 to 12/2010 in our hospital. Breakthrough IFD were identified from the database of the central pharmacy and the French administrative database (PMSI), registering final medical diagnoses of hospitalized patients. Medical data were reviewed to study proven or probable IFD, according to EORTC/MSG definition. PSC plasma concentrations (PPC) were also retrieved. Poisson models were used for statistical analysis. Two hundred and seventy nine patients received PSC prophylaxis for a median duration of 1.4 months (range 0.2-17.9). Proven (n=6)

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or probable (n=3) IFD were diagnosed in 9 cases (3.2%). IFD incidence rate per 100 person-month was 1.65 (95% CI 0.79-2.97). IFD were candidemia (Candida glabrata n=2), pulmonary invasive aspergillosis (n=3), disseminated fusariosis (n=2) and pulmonary mucormycosis (n=2). Seven deaths were reported, directly related to IFD in 3 patients (33.3%). First dosage of PPC under 0.3µg/ml was the single significant risk factor for IFD (RR 7.77, 95% CI 1.30-46.5, p=0.025). Breakthrough IFD in patients receiving PSC prophylaxis is rare but associated with a poor outcome. Low PSC plasma concentrations are associated with an increased risk of IFD

.Introduction

Despite improvement in the management of acute leukemia (AL) and allogenic hematopoietic stem cell transplantation (AHSCT), invasive fungal infection (IFD) remains an important cause of morbidity and mortality in these settings [1,2]. Identified risk factors of IFD such as prolonged and profound neutropenia, corticosteroids and immunosuppressive therapies, recent surgery, exposition to invasive devices, broad-spectrum antibiotic therapy, older age, diabetes mellitus, renal failure, viral infections and fungal colonization are often combined in patients with hematologic malignancies [3]. Poor outcome is often described in the course of IFD [2,4,5,6]. Primary prophylaxis using fluconazole has proven to prevent *Candida* infections and to reduce mortality in patients with hematologic cancers [7]. With fluconazole prophylaxis, candidemia incidence has declined, but an increase of bloodstream infections due to non-*albicans Candida* species, including fluconazole-resistant *C. glabrata* and *C. krusei*, has been reported [8]. *Aspergillus* spp. and other molds, including zygomycetes and *Fusarium* spp., have become more frequent causes of IFD [2,5,9]. New agents were subsequently developed for IFD prophylaxis, such as posaconazole (PSC), which was demonstrated to be superior to fluconazole for IFD prevention in two large controlled trials

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