International Journal of Antimicrobial Agents 50 (2017) 384–388

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Comparing the safety and efficacy of voriconazole versus posaconazole in the prevention of invasive fungal infections in high-risk patients with hematological malignancies

Ray Hachem *, Andrew Assaf, Yazan Numan, Pankil Shah, Ying Jiang, Anne-Marie Chaftari, Issam I. Raad

Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas

ARTICLE INFO

Article history:
Received 10 October 2016
Accepted 22 March 2017

Keywords:
Voriconazole
Posaconazole
Invasive fungal infections
Hematological malignancies
Cancer patients

ABSTRACT

Invasive fungal infection (IFI) is a leading cause of morbidity and mortality in immunocompromised cancer patients. New triazole-based antifungal agents have been recommended for IFI prophylaxis in these patients. This retrospective study compared the safety and efficacy of voriconazole and posaconazole as prophylaxis in patients with hematological malignancies (HM), who were admitted to The University of Texas MD Anderson Cancer Center between January 2014 and August 2015, and who were started on single antifungal prophylaxis consisting of either voriconazole or posaconazole. A total of 200 patients with hematological malignancy were evaluated, the majority of whom had acute myeloid leukemia (AML) (67%). Baseline characteristics, including malignancy status and neutropenia status, were comparable in the two groups. The duration of prophylaxis was similar in the two groups, with medians of 46 days for voriconazole and 48 days for posaconazole. There was no significant difference in breakthrough IFIs between the two groups (3% vs. 0%, $P = 0.25$). Adverse events occurred in 65% of the voriconazole group vs. 78% of the posaconazole group ($P = 0.08$). Symptomatic adverse events were more common for voriconazole than for posaconazole (6% vs. 0%, $P = 0.03$). Eleven patients discontinued voriconazole and seven patients discontinued posaconazole due to adverse events. All-cause mortality was similar in the two groups. Both agents were effective in preventing IFI in hematological malignancy, with comparable all-cause mortality rates. Symptomatic adverse events were significantly more common in the voriconazole group, whereas liver function test abnormality was more common in the posaconazole group.

1. Introduction

Invasive fungal infections (IFIs) are a leading cause of morbidity and mortality in severely neutropenic patients, particularly patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), and recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1–4]. The incidence of proven or probable mold and yeast infections among patients with leukemia can reach 24% [5], whereas the incidence after allo–HSCT is as high as 10% to 20%, and associated mortality rates range from 30% to 80% depending on the pathogen.

As IFIs have no specific clinical features (persistent fever may be the only early sign), they can be challenging to diagnose. This challenge and the high risk of mortality dictate a rationale for antifungal prophylaxis in the high-risk patient with hematological malignancy. New clinical practices for these immunocompromised patients have significantly changed the epidemiological characteristics of infectious complications, including IFIs [6–8]. To reduce the incidence of IFIs, various preventive strategies have been investigated, including infection control measures and antifungal prophylaxis, with various results [9]. Early-generation oral azoles, such as fluconazole and itraconazole, have been traditionally used for primary antifungal prophylaxis, but they have limitations in terms of the spectrum of antifungal activity, particularly against mold. In the last few years, newer antifungal agents have provided further opportunities for better tolerated and more effective antifungal prophylaxis. Posaconazole is a triazole that has been approved by the U.S. Food and Drug Administration for antifungal prophylaxis, particularly in patients with AML or MDS and allo-HSCT recipients, and it has been demonstrated to significantly affect the current use of antifungal prophylaxis [10,11]. A few studies have shown that voriconazole could be a promising prophylactic agent [12,13], but there are limited data on voriconazole use as prophylaxis for IFIs.

* Corresponding author. Department of Infectious Diseases, Infection Control and Employee Health, Unit 1460, 1515 Holcombe Blvd., The University of Texas MD Anderson Cancer Center, Houston, TX 77030.
E-mail address: rhachem@mdanderson.org (R. Hachem).

http://dx.doi.org/10.1016/j.ijantimicag.2017.03.021
0924-8579/

The selection of appropriate antifungal prophylaxis is very important in immunocompromised cancer patients at high risk of IFIs. The aim of this retrospective study was to compare the use of voriconazole vs. posaconazole for antifungal prophylaxis in terms of efficacy, adverse events and breakthrough fungal infections in neutropenic patients with hematological malignancy.

2. Patients and methods

2.1. Patient population

This retrospective study was conducted to compare the safety and efficacy of voriconazole and posaconazole in the prevention of IFIs in 200 high-risk patients with hematological malignancies or who were undergoing HSCT, who were admitted to The University of Texas MD Anderson Cancer Center between January 2014 and August 2015, and who were started on single antifungal prophylaxis consisting of either voriconazole or posaconazole.

Consecutive patients aged 13 years or older with hematological malignancies who were neutropenic, undergoing intensive induction chemotherapy or HSCT, or receiving steroids or other immunosuppressive medications, were eligible if they were prescribed either voriconazole or posaconazole for the sole purpose of prophylaxis. Exclusion criteria included patients with probable and proven invasive fungal disease per the Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer Criteria [14] and patients on dual antifungal therapy. All patients with crossover prophylaxis were excluded.

A standardized form was used to collect patient information from electronic medical records including age, sex, race, hematological malignancy type, history of HSCT, graft-versus-host disease (GVHD), weight and height. Antifungal therapy in the 30 days prior to start of prophylaxis, mucositis status and adverse events related to prophylaxis were also noted on the form. Levels of liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and alkaline phosphatase (AP), were recorded for the start and end dates of prophylaxis, and their respective peaks during prophylaxis were also recorded. The Common Terminology Criteria of Adverse Events (CTCAE) defined by the National Cancer Institute, USA was used to grade the severity of adverse events. All AEs ≥2 were recorded.

2.2. Definitions

With reference to the Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer Criteria, probable invasive fungal disease was defined as meeting at least one clinical criterion (such as having a lower respiratory tract infection with a cavity, air crescent sign or pulmonary nodule(s) with or without a halo sign on chest CT scan) in the setting of a host factor (recent history of neutropenia with an absolute neutrophil count < 500 cells/mm^3 for more than 10 days, receipt of an allogenic stem cell transplant, prolonged use of corticosteroids for more than 3 weeks at a dose equal to or greater than 0.3 mg/kg, treatment with other recognized T–cell immunosuppressants or having an inherited severe immunodeficiency), in addition to a mycological criterion (direct tests that include the presence of fungal elements from a fluid and/or tissue specimen or growth of a mold on a culture or indirect tests that include a positive galactomannan antigen). Proven invasive fungal disease includes growth of the fungus from a culture or histopathological examination confirming the presence of the fungal organism [14].

Patients received voriconazole 200 mg twice a day or posaconazole 300 mg daily (oral tablets). The minimum duration of prophylaxis was 7 days, and the maximum duration was 92 days. Patients were assessed during prophylaxis and up to 30 days after the end of prophylaxis for the development of probable or proven invasive fungal disease. Mortality rate during the above-mentioned period was also documented. The choice of antifungal prophylaxis was left at the discretion of the primary team and was administered according to the institution guidelines.

2.3. Statistical methods

Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using the Wilcoxon rank-sum test. All tests were two-sided with a significance level of 0.05. Data analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline patient characteristics

The study included 200 patients with hematological malignancy who were immunosuppressed and were started on either voriconazole or posaconazole prophylaxis between January 2014 and August 2015. The median age of the patients was 55 years. Fifty-six percent of patients were male, and 69% were white. The majority of patients had AML (67%) and had active malignancy (60%). Nearly half the patients (47%) had been neutropenic for more than 10 days prior to the initiation of prophylaxis. All the non-neutropenic patients were treated with some immunosuppressant agents. Seventeen patients (9%) had a history of HSCT prior to prophylaxis, with a median of 24 days from transplantation to initiation of prophylaxis. They all received HSCT once. Four of the 17 patients (24%) developed GVHD and were treated with high-dose corticosteroids (cumulative dose > 600 mg). Patient demographic and clinical characteristics at baseline are summarized in Table 1.

3.2. Patients receiving different prophylaxis

Of the 200 patients, 100 (50%) received voriconazole and 100 (50%) received posaconazole as antifungal prophylaxis. The median duration of prophylaxis was 46 days for the voriconazole group and 48 days for the posaconazole group. Baseline characteristics, including malignancy status, neutropenia status and prior antifungal prophylaxis, were comparable in the two groups (Table 1).

3.3. Efficacy and adverse events

Efficacy and safety of the two types of prophylaxis were evaluated (Table 2). Within 30 days after prophylaxis, 3 of the 100 patients receiving voriconazole and none of the 100 patients receiving posaconazole developed IFI (3% vs 0%, $P = 0.25$). One patient in the voriconazole group and five patients in the posaconazole group died during this time period (1% vs 5%, $P = 0.21$). No death was attributed to an IFI. A total of 11 patients in the voriconazole group had an adverse event compared with 7 patients in the posaconazole group (11% vs 7%, $P = 0.32$). Six patients in the voriconazole group and no patients in the posaconazole group experienced a symptomatic adverse event (6% vs 0%, $P = 0.029$). The six symptomatic adverse events were three gastrointestinal events, one rash and two visual disturbances. Eleven patients had to discontinue voriconazole because of visual hallucinations (two patients), hyperbilirubinemia (one patient) and transaminitis (eight patients), whereas seven patients discontinued posaconazole because of transaminitis ($P = 0.32$). Regarding liver enzymes, the two groups of patients had comparable AST, ALT, AP and bilirubin levels at baseline. However, patients in the posaconazole group had significantly higher peak bilirubin levels than those in the voriconazole group (median: 1.40