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Short communication

Micafungin as primary antifungal prophylaxis in patients presenting with acute myeloid leukemia

Micafungine comme prophylaxie antifongique primaire chez les patients atteints de leucémie aigüe myéloïde

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Abstract

Objective. – To study the efficacy and safety of micafungin for prophylaxis of invasive fungal infections in patients undergoing induction chemotherapy for acute myeloid leukemia.

Patients and methods. – A prospective observational single-center study of 41 patients from the hematology department between May 2012 and April 2015. Micafungin was administered once daily from the first day of induction chemotherapy to the end of the neutropenic phase.

Results. – Neither *Candida* nor *Aspergillus* infection was documented in our 41 patients from the first day of micafungin infusion to the end of the neutropenic phase. Patients were followed for three months after discontinuation of micafungin and none of them contracted an invasive fungal infection. Only one patient presented with grade III–IV hepatic and ionic toxicities.

Conclusion. – Micafungin is associated with a good safety profile and is an interesting option for preventing invasive fungal infections in the high-risk population of patients presenting with hematological disorders.

Keywords: Micafungin; Acute myeloid leukemia; *Aspergillus*

Résumé

Objectif. – Notre objectif était d'étudier l'efficacité et l'innocuité de la micafungine comme prophylaxie antifongique primaire chez les patients atteints de leucémie aigüe myéloïde.

Patients et méthodes. – Nous avons inclus 41 patients de mai 2012 à avril 2015. La micafungine a été administrée du premier jour de la chimiothérapie d'induction jusqu'à la fin de la période de neutropénie.

Résultats. – Aucune infection à *Candida* ou *Aspergillus* n'a été documentée chez nos 41 patients entre le premier jour de la chimiothérapie d'induction et la fin de la période de neutropénie. Trois mois après l'arrêt de la micafungine, aucun patient n'a développé d'infection fongique invasive. Un seul patient a présenté une toxicité de grade III–IV.

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Conclusion. – La micafungine est associée à un excellent profil de tolérance et semble être une option intéressante pour prévenir les infections fongiques invasives dans la population à haut risque des patients traités pour hémopathie maligne.

Mots clés : Micafungine ; Leucémie aiguë myéloïde ; *Aspergillus*

1. Introduction

Patients presenting with hematological disorders with an anticipated duration of neutropenia of more than seven days are at high risk of invasive fungal infections (IFIs) involving both *Candida* and *Aspergillus* species. IFI early diagnosis is difficult to establish and, given the high morbidity and mortality of established invasive fungal disease, primary antifungal prophylaxis is highly recommended in current guidelines (e.g., ECIL, ASBMT) [1,2]. Broad-spectrum treatments active against both *Candida* and *Aspergillus* species have an advantage over those with activity against *Candida* alone.

Posaconazole is recommended for the prevention of fungal risk in acute myeloid leukemia (AML) patients undergoing induction chemotherapy [1]. However, oral posaconazole shows great variability in terms of bioavailability and compliance [3]. Moreover, cross-resistance to azoles (fluconazole, voriconazole, posaconazole) may occur among *Candida* species and particularly *C. glabrata*. Emergent infections with resistant bacteria may thus occur in patients receiving prophylaxis with any azole drug [4,5].

This is why echinocandins such as micafungin, a recent class of antifungal agents active against *Candida* and *Aspergillus* species, are increasingly used for prophylaxis [6–8]. Micafungin, unlike fluconazole, does not interact with drugs metabolized via the cytochrome P450 [9]. Dose adjustment is also not required in patients presenting with renal impairment.

2. Patients and methods

We conducted a prospective observational single-center study at the Hematology and Cellular Therapy Department of the University Hospital of Marseille (Hôpital de la Conception). We aimed to study the efficacy and safety of micafungin in preventing IFIs in AML patients undergoing induction chemotherapy in routine practice. All patients requiring first induction chemotherapy for AML (de novo AML or AML secondary to myelodysplastic or myeloproliferative syndromes) and treated with primary prophylactic micafungin were included in the study. Patients had to be free of invasive fungal disease at the time of enrolment.

Micafungin was administered once daily as a one-hour infusion (50 mg/day) on the first day of induction therapy for AML. Patients were monitored after the first day of induction for galactomannan antigenemia at least once per week. A CT scan was performed in case of persistent fever for at least five days following broad-spectrum empirical antibacterial therapy. Micafungin was discontinued when absolute neutrophil count (ANC) had reached $>1500/mm^3$ in the absence of fever and IFI.

Criteria for proven and probable infection were consistent with those for IFI described by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer, National Institute of Allergy, and Infectious Diseases Mycoses Study Group. A proven fungal infection was defined as a biopsy-proven invasive or disseminated infection. A probable pulmonary aspergillosis was diagnosed by lower respiratory tract diagnostic tests and was defined by the presence of fungi as well as clinical and radiographic findings. Suspected fungal infection was defined as fever (temperature >38 °C) lasting for 96 h during the neutropenic phase despite a broad-spectrum antibacterial therapy. Suspected fungal infection led to empirical antifungal therapy [10].

A successful treatment was defined as the absence of a proven or probable systemic fungal infection until the end of the neutropenic phase. The use of systemic antifungal agents for the treatment of suspected fungal infections was considered a failure. Safety analyses included standard micafungin adverse events: hepatic and ionic grade III–IV toxicity according to the 2009 WHO classification, and no hematopoietic reconstitution.

Induction of chemotherapy was performed using daunorubicin (90 mg/m^2/day, 3 days) and cytarabine (200 mg/m^2/day, 7 days) in patients aged < 65 years. Idarubicin (8 mg/m^2/day, 5 days) and cytarabine (100 mg/m^2/day, 7 days) were used in patients aged > 65 years. Refractory patients (bone marrow blasts > 5%) at day 15 after first induction chemotherapy received a second-line chemotherapy.

All patients received the same supportive care during the whole study period. *P. jiroveci* pneumonia prophylaxis consisted of trimethoprim (160 mg) + sulfamethoxazole (800 mg) administered twice weekly in all patients. Trimethoprim–sulfamethoxazole was initiated after induction of chemotherapy, but at the end of the neutropenic phase as soon as ANC reached $>1000/mm^3$. The objective was to avoid slowing down the hematopoiesis recovery. Prophylaxis against HSV included oral valacyclovir (500 mg × 2/day) during micafungin treatment.

3. Results

Overall, 41 patients from our department were enrolled between May 2012 and April 2015.

Patients received a median of 30 micafungin infusions (range 7–40). Neither *Candida* nor *Aspergillus* infection was documented in our 41 patients between the first day of the induction regimen and until ANC reached $>1500/mm^3$. Patients were