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LETTER TO THE EDITOR

Primary antifungal prophylaxis with micafungin after allogeneic hematopoietic stem cell transplantation: a monocentric prospective study

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Dear Editor,

Invasive fungal diseases (IFDs) after allogeneic hematopoietic stem cell transplantation (alloHSCT) are mainly caused by *Aspergillus* and *Candida*. Primary antifungal prophylaxis (PAP) with fluconazole is recommended for 100-day post-alloHSCT [1]. Candida infections have evolved epidemiologically as azole-resistant species have increased [2, 3] and fluconazole does not prevent *Aspergillus* infections. Micafungin is active against most *Candida* and *Aspergillus* species, with similar or superior overall efficacy over fluconazole during the neutropenic phase in hematological patients [3–8].

Due to its larger antifungal spectrum and lower interactions with immunosuppressive agents compared with fluconazole, we tested micafungin as a PAP through a monocentric prospective study focusing on alloHSCT recipients at high risk of IFDs.

From November 2013 to September 2014, we included 26 consecutive recipients of a first unrelated alloHSCT after myelo-ablative or sequential conditioning, and retrospectively compared them with a previous 36-patient cohort with identical inclusion/exclusion criteria receiving fluconazole PAP. The primary objective was the incidence of invasive candidiasis. The incidences and reasons for antifungal withdrawal were compared between both groups.

Antifungal treatment was initiated at the beginning of the conditioning regimen (micafungin 50 mg/day) or at D + 1 (fluconazole 400 mg/day). IFDs were recorded from transplantation until antifungal withdrawal or D + 60. Prophylaxes were withdrawn for: neutrophil recovery; acute graft-versus-host disease treated with steroids necessitating anti-*Aspergillus* prophylaxis; diagnosis of proven/probable/possible IFDs (EORTC/MSG criteria) [9]; and indication for empirical antifungal treatment (fluconazole group only). Blood galactomannan was performed biweekly. In cases of febrile neutropenia lasting > 72 h despite large-spectrum antibiotherapy, a sinus-thoraco-abdomino-pelvic CT scan was performed. If radiological exams were normal, micafungin was continued until engraftment. Fluconazole was withdrawn and replaced by an empirical antifungal treatment (caspofungin or liposomal amphotericin B). Inverse probability of treatment weighting was used to limit confounding bias in outcome comparisons. The study was conducted according to the Helsinki declaration.

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Table 1 IFDs diagnosed in both populations: characteristics and evolution with treatment

Pat	Sex Age	Diag	Conditioning	Stem cell source	HLA matching	D + 60 status	Death	Cause	ATF	Ttt length (days)
1	F 36	ALL CR1	MAC	PBSC	MUD	Alive			Mica	24
2	M 40	ALL CR1	MAC	PBSC	MUD	Alive			Mica	30
3	M 40	ALL CR1	MAC	PBSC	MUD	Alive			Mica	18
4	F 18	ALL CR1	MAC	BM	MUD	Alive			Mica	15
5	M 39	ALL CR1	MAC	PBSC	MMUD	Alive			Mica	26
6	M 19	AML CR1	MAC	PBSC	MMUD	Alive			Mica	15
7	M 19	ALL CR1	MAC	CB	MMUD	Dead	D + 53	GVH and infection	Mica	12
8	F 35	NHL CR1	MAC	PBSC	MUD	Alive			Fluco	24
9	M 15	ALL CR2	MAC	PBSC	MUD	Alive			Fluco	10
10	M 34	NHL PR2	MAC	BM	MUD	Alive			Fluco	18
11	M 25	ALL CR2	MAC	PBSC	MMUD	Alive			Fluco	12
12	M 16	ALL CR3	MAC	CB	MMUD	Dead	D + 74	Infection	Fluco	5
13	F 24	AML CR1	Sequential	PBSC	MUD	Alive			Fluco	1

Pat	CT scan for febrile neutropenia	D+	Results	Blood GM	IFD diagnosis D+	IFD		Evolution	Treatment
1	Yes	19	Bilateral pulmonary micronodules	Neg	19	Possible	Pulmonary IFD	Favorable	Voriconazole
2	No		N/A	Neg	21	Proven	*C. parapsilosis* candidemia	Favorable	Voriconazole
3	Yes	19	Normal	Neg	13	Proven	C. parapsilosis candidemia	Favorable	Voriconazole
4	Yes	14	Hepatomegaly, several hypodense liver lesions with subcutaneous infiltration	Neg	15	Proven	Mucor indicus liver infection	Favorable	L-Amb + surgery
5	Yes	19	Normal	Neg	22	Proven	*C. albicans* candidemia	Favorable	L-Amb
6	Yes	10	Normal	Neg	13	Proven	Fusarium solani (blood + skin)	Favorable	L-Amb + voriconazole
7	Yes	12	Micronodules and ground glass opacities	Neg	10	Possible	Pulmonary IFD	Favorable	Voriconazole
8	Yes	18	Right inferior lobe condensation	Pos	25	Probable	Pulmonary aspergillosis	Favorable	L-Amb
9	No		N/A	Neg	11	Proven	*C. krusei* (blood + skin)	Favorable	Caspofungin
10	No	18	Bilateral pulmonary nodules with ground glass halo	Pos	19	Probable	Pulmonary aspergillosis	Favorable	Voriconazole
11	Yes	15	Left basal lesion	Neg	13	Possible	Pulmonary IFD	Favorable	Caspofungin
12	Yes	8	Ground glass opacities superior right lobe	Neg	6	Probable	Pulmonary aspergillosis	Favorable	Caspofungin
13	Yes	1	Left upper lobe: condensation + ground glass opacities	Neg	1	Possible	Pulmonary IFD	Favorable	Caspofungin

Pat, patient; *F*, female; *M*, male; *ALL*, acute lymphoblastic leukemia; *AML*, acute myeloblastic leukemia; *CR*, complete remission; *PBSC*, peripheral blood stem cell; *BM*, bone marrow; *CB*, cord blood; *MUD*, matched unrelated donor; *MMUD*, mismatched unrelated donor; *GVH*, graft-versus-host-disease; *Fluco*, fluconazole; *Mica*, micafungin; *Ttt*, treatment; *GM*, galactomannan; *Pos*, positive; *Neg*, negative; *L-Amb*, liposomal amphotericin B

Two-month survival was 92% and 94% for the micafungin and fluconazole groups, respectively. Four candidemia were diagnosed (micafungin, $n = 3$, fluconazole, $n = 1$), but no cases of disseminated *Candida* infection with negative blood culture. In the micafungin group, we diagnosed two proven IFDs and two possible pulmonary IFDs; in the fluconazole group, three probable pulmonary aspergilloses and two possible pulmonary IFDs (Table 1).

The cumulative incidences of candidemia and other IFDs were not significantly different between both groups ($p = 0.46$ and $p = 0.56$, respectively).

We observed a high incidence of IFDs in the micafungin group (proven 19%; proven, probable, and possible 27%), compared with previous reports of alloHSCT recipients. That finding could be related to our patients' characteristics (high risk of IFDs). No local problem explaining this high number of breakthrough IFDs was identified, and we did not observe more IFDs due to rare fungi after study withdrawal. While we cannot exclude a hazard effect during the study period, we can however hypothesize that the selective pressure arising from micafungin may have led to the emergence of rare fungi. Micafungin cannot be recommended as PAP in high risk IFDs patients after alloHSCT (risk of breakthrough IFDs caused by resistant fungi).

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no competing interests.

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