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Use of micafungin as antifungal prophylaxis in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) in Spain (GETH-MIC)

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ABSTRACT

Introduction. The fungal infections remain an important problem in the allogeneic stem cell trasnsplantation (allo-SCT) setting and thus, anti-fungal prophylaxis is commonly used. The antifungal drug should offer activity, at least against *Candida* and *Aspergillus* spp., a good safety profile and low probability interactions. Micafungin could theoretically fulfill these requisites. The aim of the study was to describe the experience with micafungin as primary prophylaxis in patients undergoing allo-SCT in a cohort of Spanish centres, and to evaluate its efficacy and tolerability in this population.

Material and methods. Retrospective multicentre observational study including all consecutive adult patients admitted for allo-SCT in participating centres of the Grupo Español de Trasplante Hematopoyético (GETH), from January 2010 to December 2013, who received micafungin as primary prophylaxis during the neutropenic period.

Results. A total of 240 patients from 13 centres were identified and 159 patients were included for the analysis. Most patients (95.6%) received 50 mg/day of micafungin. During the follow-up, 7 (4.4%) patients developed breakthrough invasive fungal disease, 1 proven and 6 probable; one patient discontinued the drug because of serious drug interactions. Prophylaxis with micafungin was considered effective in 151 (94.9%) patients.

Conclusions. According to our experience, micafungin is an appropriate alternative for antifungal prophylaxis in patients undergoing an allo-HSCT, because its efficacy, its low profile of drug interactions and side-effects.

Key-words: Stem cell transplantation, micafungin, prophylaxis.

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Profilaxis antifúngica con micafungina en pacientes que reciben un trasplante alogénico de progenitores hematopoyéticos (alo-TPH) en España (GETH-MIC)

RESUMEN

Introducción. Las infecciones fúngicas siguen representando un problema en el trasplante alogénico de progenitores hematopoyéticos (alo-TPH) por lo que es habitual el uso de profilaxis antifúngica en estos pacientes. El tratamiento antifúngico debe presentar al menos actividad frente a *Candida* y *Aspergillus* spp, un buen perfil de seguridad y baja probabilidad de infecciones, siendo micafungina una de las opciones que podría cumplir todos estos requisitos. El objetivo del estudio fue describir la experiencia con micafungina como profilaxis primaria en pacientes sometidos a alo-TPH en una cohorte de hospitales españoles, y evaluar su eficacia y seguridad en esta población.

Material y métodos. Estudio retrospectivo multicéntrico observacional consecutivo de todos los pacientes adultos ingresados para alo-TPH en los centros del Grupo Español de Trasplante Hematopoyético (GETH) desde enero de 2010 a diciembre de 2013 y que recibieron micafungina como profilaxis primaria durante el periodo de neutropenia.

Resultados. Se identificaron 240 pacientes de 13 hospitales y 159 fueron incluidos para el análisis. La mayoría (95.6%) de ellos recibieron dosis de 50mg/día de micafungina. Durante el seguimiento, 7 (4.4%) pacientes desarrollaron infecciones de brecha, 1 probada y 6 probables; en un paciente se suspendió el tratamiento por interacciones medicamentosas graves. La profilaxis con micafungina se consideró efectiva en el 94,9% de los pacientes (151 de 159).

Conclusiones. En base a nuestros resultados, consideramos que Micafungina es una buena alternativa como profilaxis antifúngica en pacientes sometidos a alo-TPH, por su eficacia, el bajo riesgo de interacciones y de efectos adversos.

Palabras clave: trasplante de células madre, micafungina, profilaxis.

INTRODUCTION

Invasive fungal infection (IFI) is an important cause of morbidity and mortality in allogeneic haematopoietic stem cell transplant (allo-HSCT) recipients [1, 2]. Although other fungi such as *Zygomycetes*, *Fusarium* spp. and *Scedosporium* spp. are being increasingly reported as important pathogens in HSCT recipients, the most frequent infections remain those related to *Aspergillus* spp. and *Candida* spp. [3].

The incidence of invasive *Candida* spp. and *Aspergillus* spp. infection is between 5% and 4–15%, with mortality rates around 30–40% in invasive candidiasis and up to 40-80% for *Aspergillus* infection [4]. Because early microbiological diagnosis is usually difficult to obtain, therapeutic strategies of prophylaxis or empirical treatment have been developed. The use of the different formulations of amphotericin B [5], voriconazol or posaconazole in this setting have shown utility, but are also associated with some toxicity and potential drug interactions which difficult their use in some patients.

Echinocandins are highly effective antifungal agents against *Candida* and *Aspergillus* spp., [6, 7]. that have demonstrated their efficacy in fungal infection prophylaxis and neutropenic fever treatment [8-10]. Micafungin provides, compared to other echinocandins, better activity against some *Candida* spp. (specially *C. glabrata*) and also *Aspergillus* spp. [7, 11]. The drug has a convenient once-daily dosage regimen and is associated with relatively few drug-drug interactions [12], positioning micafungin as a good alternative in those patients who need concomitant treatments or present moderate hepatic or renal dysfunction. Several studies have exposed their experience with micafungin as prophylaxis during neutropenia in hematologic patients, including randomized controlled trials [13, 16], and recent guidelines focused on antifungal prophylaxis also supported its use in neutropenic patients after HSCT [17].

The aim of this study was to describe the experience with micafungin as primary prophylaxis during the neutropenic phase in patients undergoing allo-HSCT in a cohort of Spanish transplant centres, and to evaluate its efficacy and tolerability in this population.

MATERIAL AND METHODS

Study design. This is a retrospective multicentre observational study including all consecutive adult patients admitted for allo-HSCT in 13 centres pertaining to the Grupo Español de Trasplante Hematopoyético (GETH) and the European Society for Blood and Marrow Transplantation (EBMT), from January 2010 to December 2013, who received micafungin as primary prophylaxis during the transplant. Patients that received less than 5 days of micafungin were excluded from the analysis. Only patients that received micafungin during the peri-transplant period (15 days before or after the infusion day) were included; patients who received prophylaxis with micafungin in the context of graft versus host disease (GVHD) were not considered for the analysis.

Study variables and data collection. Demographic, clinical, laboratory, microbiological and radiologic data, clinical course and mortality were retrospectively recorded from each patient. Patients were followed-up until hospital discharge. All clinical data of patients submitted to HSCT in Spain are routinely included in the EBMT registry database as a part of a continuous observational study. The data included in this study have been obtained from this registry. The data contained are loaned by patients under informed consent signed by them at the time of transplantation. The Ethics Committee of the GETH approved this study.

Definitions and statistical analysis. Possible, probable or proven IFI was considered according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [1]. Failure of prophylaxis was considered in those patients who developed breakthrough IFI during prophylaxis or in the 30 first days after transplantation or the treatment was discontinued because of toxicity or interactions mild or moderate side effects were considerate when no need of treatment discontinuation was needed. Conversely, severe side effects were considered in those cases where micafungin needed to be discontinued.

Continuous variables are expressed as the median and interquartile range (IQR) or mean and standard deviation as appropriate. Statistical analyses were performed using the statistical software package IBM SPSS Statistics for Macintosh, Version 21.0. Armonk, NY: IBM Corp.

RESULTS

Baseline characteristics. During the study period, data from 240 patients from 13 HSCT units belonging to the GETH group were collected. Eighty-one patients were excluded for different reasons (figure 1). Finally, 159 patients were included for the analysis. Ninety-four (59%) were men. Mean age was 48 (± 13) years. All the demographic characteristics of the patients at baseline are summarized in table 1.

Prophylaxis with micafungin and outcome. The median (range) days of prophylaxis with micafungin were 18 (13-24) days. The main reason to micafungin discontinuation was instauration of fungal empirical therapy in 7 (4.4%) patients. There was only 1 (0.6%) patient who discontinued because of toxicity. The most common dose used by the centres was 50 mg/day, in 152 (95.6%) patients, while (4.4%) received 100 mg/day.

Breakthrough IFI was unfrequent with 1 and 6 proven or probable IFI documented through the follow-up. Data regarding these patients are summarized in table 2. The median days of treatment with micafungin in these patients was 14 (10-25) days at a dose of 50 mg/day. Five of these patients died: two due to multiple organ failure, 1 patient because of sinusoidal obstruction syndrome and one because of staphylococcal septic shock. Six other patients died because of different complications related to the underlying disease and its treatment. None of the deaths was attributed to fungal infection.

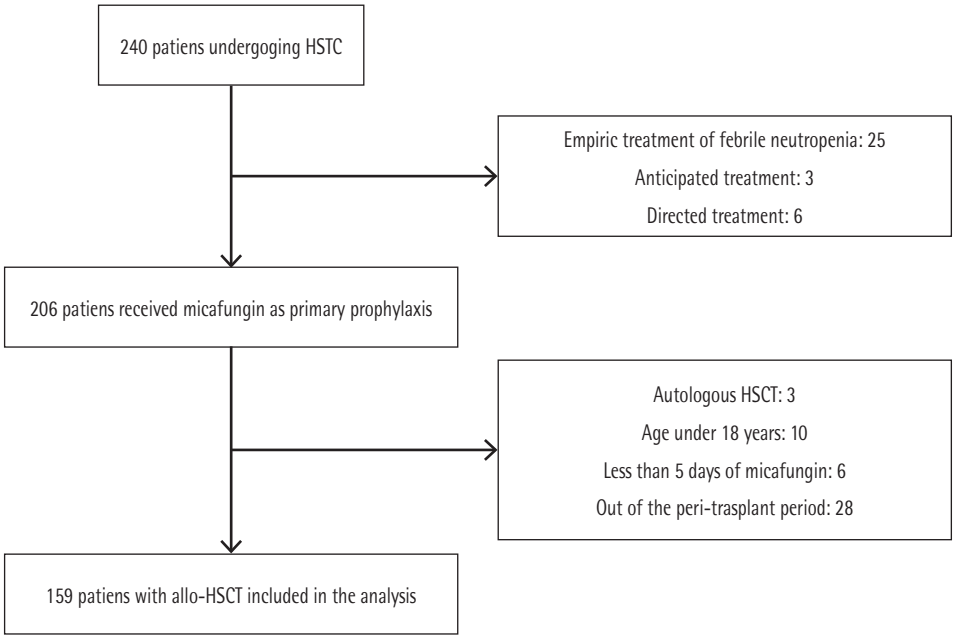

Figure 1 Patient selection flowchart

HSCT: hematopoietic stem cell transplantation

Table 1 Demographic characteristics of all patients (n =159) with allo-HSCT.

Male sex	94 (59.1)
Age, years, mean (SD)	47.8 (±12.7)
Underlying hematologic disease	
Leukaemia	82 (51.6)
Lymphoma	34 (21.4)
Myelodysplastic syndrome	26 (16.4)
Multiple myeloma	8 (5)
Other pathologies	9 (5.7)
Type of allo-HSCT	
Peripheral blood	151 (95)
Bone marrow	6 (3.8)
Umbilical cord	2 (1.3)
Median (IQR) days of neutropenia (< 500 cells x 10^9/L)	16 (12 – 20)
Patients with neutropenia (< 500 cells x 10^9/L) during > 10 days	130 (81.8)

Results are expressed in n (%) unless otherwise stated.
Allo-HSCT: allogeneic hematopoietic stem cell transplantation

Side effects. Only one patient presented serious drug interactions that obliged micafungin cessation consistent in drug-drug interaction with concomitant therapies that were not referred. Two other patients presented mild liver enzyme elevation during treatment but no need of antifungal treatment discontinuation was needed. Overall, prophylaxis with micafungin was considered effective. This is no fungal infection and no requirement to stop de drug because of toxicity/interactions in 151 (94.9%) of the patients.

Prophylaxis efficacy. Besides those patients who developed probable/proven IFI or toxicity, 24 patients changed the antifungal prophylaxis because of suspected IFI, although finally only in seven of them a probable or proven IFI was detected. Therefor micafungin was considered effective in 151 (94.9%) patients.

DISCUSSION

Our study, in different Spanish centres, indicates that the use of micafungin as prophylaxis in the allo-HSCT is well tolerated and effective. The rate of prophylaxis failure (combination of development of IFI or requirement to change the antifungal therapy because of drug-drug interactions) was 5.1%, while it was successful in 151 (94.9%) patients.

Micafungin is a semi-synthetic lipopeptide echinocandins which blocks the synthesis of 1,3-b- D-glucan, a major component of the cell wall of most fungal cells [18]. Its convenient once-daily dosage regimen, the good safety and its low drug-drug interactions profile, [12, 19] have positioned it as a good alternative in patients undergoing allo-HSCT during the neutropenic phase. In 2014 Ziakas *et al.* published a meta-analysis to evaluate the comparative effectiveness of systemic antifungal prophylaxis in HSCT recipients, including data of 4,823 patients from twenty studies considered evaluable. Although

Table 2 Clinical characteristics and putcome of breackthrough IFI.

Case	Underlying disease	Type of HSCT	Micafungin dose (mg/d)	Duration (days)	Days from micafungin initiation to IFI diagnosis	Compatible radiological findings with IFI	Mycological criteria for IFI	EORTC IFI grade	Change to directed antifungal treatment	Outcome	Cause of death	IFI-related death
1	Leukaemia	UC	50	29	10	Yes	Positive GMN	Probable	No	Death	MOF	No
2	Leukaemia	PB	50	12 + 11	N/A	Yes	Positive GMN	Probable	Yes[a]	Death	*S. aureus* bacteremia	No
3	Lymphoma	PB	50	14	13	Yes	Positive GMN	Probable	Yes[b]	Successful	--	--
4	MDS	PB	50	25	17	Yes	Positive GMN	Probable	Yes[c]	Successful	--	--
5	Lymphoma	PB	50	6 + 15	N/A	Yes	Positive GMN	Probable	Yes[d]	Death	MOF	No
6	Lymphoma	PB	50	10	10	Yes	Positive GMN *Aspergillus flavus* in *sputum sample*	Probable	Yes[e]	Death	VOD	No
7	Leukaemia	PB	50	25	24	No	*Fusarium solani* in skin biopsy	Proven	Yes[b]	Successful	--	--

HSCT: Hematopoietic stem cell transplant; IFI: Invasive fungal infection; MDS: myelodysplastic syndrome; UC: umbilical cord; PB: peripheral blood; BM: bone marrow; GMN: galactomannan; MOF: multiple organ failure failure; VOD: veno-occlusive disease; N/A: not applicable.

[a]Case 2 received 12 days of primary prophylaxis with micafungin, substituted for liposomal amphotericin during 11 days, changed again to micafungin at dose of 50mg/d during 11 days, and after changed again to liposomal amphotericin during 20 days and finally to caspofungin for 4 days. The first positive galactomannan was at the end of treatment with caspofungin (24 days after the last dose of micafungin). Treating clinicians considered failure of prophylaxis with micafungin.

[b]Not specified.

[c]To voriconazole.

[d]Case 5 received initially 6 days of primary prophylaxis with micafungin. He developed fever and a lobar infiltrate evident on chest x-ray and directed treatment with liposomal amphotericin was started for 19 days. Prophylaxis with micafungin was restarted at dose of 50mg/d. After 15 days, bilateral nodules and pleural effusion compatible with IFI were evident on the CT scan. Two determinations for GMN were positive and directed treatment with caspofungin was started. Treating clinicians considered failure of prophylaxis with micafungin.

[e]To liposomal amphotericin.

fluconazole continued to be the most widely used agent, micafungin proved to be more effective than fluconazole for the prevention of all mold infections and invasive aspergillosis, reducing the need for empiric antifungal treatment [20]. In the same way Wang et al. analysed data from ten randomized controlled trials involving 2,837 patients with the aim to compare the efficacy and safety between echinocandins and triazoles for the prophylaxis and treatment of fungal infections. The results positioned echinocandins to be as effective and safe as triazoles for the prophylaxis and treatment of patients with fungal infections [21].

Besides efficacy, side-effects with equinocandins, including micafungin, are less common compared to azoles, which conditions better tolerance [15, 21, 22]. All these facts have conducted some guidelines focused on antifungal prophylaxis to recommend the use of micafungin with equal strength to other prophylaxis strategies during the neutropenic phase following allo-HSCT [17, 23]. Nevertheless to date, few observational studies have evaluated the role of micafungin as prophylaxis during the pre-engraftment period of allo-HSCT in day-to-day clinical practice in adult population. Hirata et al. carried out a retrospective study to assess the antifungal prophylactic efficacy, safety, and tolerability of micafungin, 150 mg daily, in a group of patients with haematological malignancies undergoing chemotherapy or HSCT. The strategy led to a significant decrease in IFI with few side effects. However, it must be borne in mind that the results with micafungin were compared to a group of patients who did not receive systemic antifungal prophylaxis [14]. Nachbaur *et. al.* described the results of another retrospective cohort involving one hundred patients with different haematological malignancies at risk for IFI, including patients undergoing allo-HSCT, who received primary antifungal prophylaxis with micafungin at a daily doses of 50 mg during neutropenia. Compared to a historical cohort with posaconzale, micafungin was at least as effective in preventing IFI, with an incidence of proven and probable breakthrough IFI of 3-6% in both groups [24]. Finally, two prospective observational studies have been published in the last years. El-Cheikh *et. al.* carried an observational single-centre trial with 26 patients receiving allo-HSCT from a French hospital who received prophylaxis with micafungin 50 mg/daily, with no *Candida* spp. and/or *Aspergillus* spp. breakthrough infections documented an no drug-related adverse events [25]. More recently, data from a prospective multicentre post-marketing observational surveillance study to assess the safety and efficacy of micafungin in Japanese patients undergoing HSCT. Among 241 patients, breakthrough IFI was documented in 4.4% of the cases. Unlike the previous studies, adverse drug reactions were much more frequent (36%), mainly as hepatobiliary disorders [26].

Our findings, in accordance with other series, show that patients who receive an allo-HSCT can receive micafungin as first-line prophylaxis for IFI, with success rates of approximately 95%. There are two further points in our study that we consider remarkable. First, according to our results, a dose of micafungin 50 mg/daily seems effective in preventing IFI in this high-risk population of patients undergoing allo-HSCT, with a good safety and tolerability profile. These results are consistent with other authors experience [27]. On the other hand, our experience with regard to side effects with micafungin has been quite satisfactory, with only one case of documented serious adverse effect in 159 patients completing a micafungin-based regimen. This factor suggests an advantage of micafungin, which should be taken into account in considering other treatments used previously.

Our study's limitations are those inherent to a retrospective design. Nevertheless, it is, to our knowledge, the only series published to date with micafungin as primary prophylaxis in allo-HSCT recipients in Spain in a very homogeneous group of patients. This posits a useful alternative in day-to-day clinical practice.

In conclusion, according to our experience, micafungin, 50mg/daily, is an appropriate alternative for antifungal prophylaxis in patients undergoing an allo-HSCT, because it's efficacy, its low profile of drug interaction and side effects.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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