Official journal of the Spanish Society of Chemotherapy

Original

Carlos Vallejo[1]
Jesús Fortún[2]
and the Study Group for IFI management

Strategies for the management of invasive fungal infections due to filamentous fungi in high-risk hemato-oncological patients

[1]Hospital Donostia, Gipuzkoa, Spain
[2]Hospital Universitario Ramón y Cajal, Madrid, Spain

Article history
Received: 20 November 2018; Accepted: 26 November 2018

ABSTRACT

Introduction. In recent years, the introduction of new antifungals for the prevention of invasive fungal infections (IFIs) in hemato-oncological patients, particularly extended-spectrum azoles, has led to a change in the diagnostic and therapeutic strategies for established or suspected breakthrough IFI. The aim of the study was to identify the diagnostic and therapeutic strategies used in the management of IFIs in hemato-oncological patients in Spain, and to assess compliance with the recommendations of the consensus documents and clinical practice guidelines.

Patients and Methods. An online, anonymous, cross-sectional survey was conducted between January and September 2016 involving 137 specialists from third-level hospitals in Spain with Departments of Hematology that regularly deal with IFIs.

Results. Galactomannan test was available to 95.6% of specialists, and was used in 61.7% of the cases for diagnostic confirmation and early treatment. The (1 → 3) β-D-glucan test was only available to 10.2%. A total of 75.3% of the participants estimated the incidence of breakthrough IFI due to filamentous fungus as being 1-10%. In turn, 83.3% of the participants decided a change in antifungal class after failure of prophylaxis, in concordance with the recommendations of the national and international consensus documents.

Conclusions. The present study, the first of its kind conducted in Spain, shows that a high percentage of the medical professionals implicated in the management of hemato-oncological patients at high risk of suffering IFIs follow the recommendations of the national and international consensus documents and guidelines.

KEY WORDS: Invasive fungal infection, Filamentous fungi, *Aspergillus*, Epidemiology, Diagnosis, Treatment.

Correspondence:
Carlos Vallejo
Hospital Donostia
Begiristain Doktorea Pasealekua, 109,
20014 Donostia,
Gipuzkoa, Spain
Email: carlosvallej@gmail.com

Estrategias para manejo de la infección fúngica invasora por hongo filamentoso en el paciente hematooncológico de alto riesgo

RESUMEN

Introducción. La incorporación, en los últimos años, de nuevos antifúngicos como profilaxis de la infección fúngica invasora (IFI) en el paciente hematooncológico, especialmente el uso de azoles de espectro extendido, ha supuesto un cambio en la estrategia de diagnóstico y de tratamiento de la IFI de brecha o de su sospecha. Los objetivos del estudio fueron identificar las estrategias diagnósticas y terapéuticas que se están empleando en el abordaje de la IFI en el paciente hematooncológico en España y evaluar el seguimiento de las recomendaciones recogidas en los consensos y guías de práctica clínica.

Métodos. Encuesta online, anónima y transversal realizada entre los meses de enero y septiembre de 2016 con la participación de 137 especialistas de centros hospitalarios de todo el territorio español que dispongan de Servicios de Hematología con experiencia en el abordaje de las IFIs.

Resultados. El 95,6% de los especialistas tienen a su disposición el test del galactomanano, siendo empleado en el 61,7% de los casos para la confirmación diagnóstica y el inicio de terapia precoz. La disponibilidad de la prueba del (1 → 3) β-D-glucano es de solo un 10,2%. El 75,3% de los participantes estima que la incidencia de la IFI de brecha por hongo filamentoso en sus Servicios se sitúa entre un 1-10%. El 83,3% de los participantes opta por cambiar de familia de antifúngicos tras el fracaso de la profilaxis en consonancia con las recomendaciones de los consensos nacionales e internacionales.

Conclusiones. El presente estudio, primero de estas características realizado en España, muestra que la comunidad médica implicada en la atención del paciente hematooncológico de alto riesgo de IFI sigue las recomendaciones recogidas en consensos nacionales y guías internacionales.

Palabra clave: infección fúngica invasora, hongos filamentosos, *Aspergillus*, epidemiología, diagnóstico, tratamiento.

INTRODUCTION

Invasive fungal infections (IFIs) due to filamentous fungi are a very serious and potentially fatal complication in patients with hemato-oncological diseases [1]. In fact, the mean mortality rate associated with invasive aspergillosis (IA) may exceed 50% in patients with malignant blood diseases and in hematopoietic transplant recipients [2].

The introduction of promising diagnostic techniques and the relative expansion in the number of antifungals has diversified the therapeutic strategies (prophylaxis and early treatment) [3]. However, the poor sensitivity and positive predictive value of some of these techniques in certain circumstances, and the potential delay in starting treatment due to logistical reasons, cause the management of IFIs to remain a challenge [1,4,5]. Because of this, different national scientific societies have developed recommendations to help clinicians improve outcomes [3,6].

The aim of this study was to know the diagnostic and therapeutic strategies currently used for the management of IFIs in hemato-oncological patients in Spain, and to determine whether clinicians adequately follow the recommendations of the consensus documents and clinical practice guidelines in Spain.

METHODOLOGY

An online, anonymous, cross-sectional, multicenter survey was conducted between January and September 2016 involving 137 healthcare professionals that regularly deal with IFIs due to filamentous fungi in high-risk hemato-oncological patients (staff: 79.8%; residents: 20.2%). The participants were from all regions of the country. Specifically, 84.8% of the specialists worked at large university hospitals in Barcelona (24.8%), Madrid (20.8%), Valencia (18.4%), Malaga (4.8%), Las Palmas de Gran Canaria (4.0%), Palma de Mallorca (4.0%), San Sebastián (4.0%) and Zaragoza (4.0%).

Most of the consulted professionals were specialists in Hematology (71.2%), though professionals from other medical specialities (particularly Infectious Diseases, Microbiology and Pediatrics) also participated. The median professional experience of the participants was 10 years (range: 1-45 years).

The questions of the survey (9 in total), developed by the study coordinators, were divided into three distinct sections: Epidemiology and Risk Factors (3 questions), Diagnosis (2 questions) and Treatment (4 questions).

RESULTS

Epidemiology and risk factors

1.- With regard to *Aspergillus* spp. resistance, choose the answer(s) that you feel most appropriate (multiple answers are allowed).

Answers provided by the coordinators: a) Resistance is more common to azoles than to amphotericin B; b) Resistance to azoles is more common in the Netherlands than in Spain; c) Resistance to azoles is more common in cryptic species (not *fumigatus*); d) The most frequent mechanism of azole resistance is the TR34/L98H mutation (*Cyp51A*).

Comment: Triazoles constitute the basis for the prevention and treatment of infections caused by *Aspergillus* spp. In recent years, the relative increase in *A. fumigatus* resistance to azoles has represented a significant challenge for the effective management of aspergillosis [7]. In contrast, the risk of development of resistance to amphotericin B in the treatment of aspergillosis in particular and severe invasive mycoses in general is low [8,9]. In addition, in hematologic patients, infection due to *A. fumigatus* is associated with higher secondary azole resistance rates than in critically ill patients [10]. The incidence of non-*fumigatus Aspergillus* species as human pathogens has increased significantly in recent years [11]. In the study published by Lamoth et al., most of the breakthrough IFIs due to *Aspergillus* spp. in patients receiving broad-spectrum azole prophylaxis were cryptic species (*A. ustus* and others) and intrinsically resistant to azoles [12]. The FILPOP study, involving the participation of 29 Spanish hospitals, showed that 34% of the isolated *Aspergillus* species were not *fumigatus*, and that up to 10% were cryptic species [13]. The incidence of non-*fumigatus Aspergillus* species in the United States is about 36%, and of these 10% are cryptic species [14]. The main azole resistance mechanism described for *A. fumigatus* is the presence of the TR34/L98H mutation of the *Cyp51A* gene, responsible for expression of the target enzyme lanosterol-14α-demethylase, upon which the different drugs in this class of antifungal agents act [15-18]. Based on the international multicenter study by van der Linden et al., the secondary triazole resistance rate of *Aspergillus* spp. ranges from 0.6-4.2% - the most common cause being the presence of the TR34/L98H mutation [19]. The secondary azole resistance rate of *A. fumigatus* in Spain is low, though further susceptibility studies are needed to determine the best treatment option [20].

Result of the survey: The vast majority (93.4%) of the participants agreed that the azole resistance rate of *Aspergillus* spp. is greater than the amphotericin B resistance rate. In addition, up to 87.6% of the participants agreed that azole resistance is more common in cryptic *Aspergillus* (non-*fumigatus*) species. On the other hand, 76.6% of the specialists considered the main azole resistance mechanism of *Aspergillus* spp. to be the TR34/L98H mutation (*Cyp51A*). Lastly, most of the members of the panel (71.5%) considered the prevalence of secondary resistance of *Aspergillus* spp. to be higher in the Netherlands than in Spain.

2.- What is the incidence of breakthrough IFIs (proven, probable and possible) due to filamentous fungi in your Department?

Answers provided by the coordinators: a) 0%; b) 1-5%; c) 6-10%; d) 11-15%; e) Not sure.

Comment: Breakthrough IFI is defined as IFI occurring in a patient who has been treated with antifungal drugs during at least 3-5 days for prophylactic or therapeutic purposes [21]. While the use of antifungal prophylaxis has been able to reduce the incidence of IFIs in high risk patients, breakthrough fungal infections and their associated morbidity and mortality still persist [12]. Hemato-oncological patients represent a population at risk of IFI due to filamentous fungi, with an incidence ranging from 0.5% (multiple myeloma) to 12% (acute myeloid leukemia [AML]) [22]. The incidence of invasive pulmonary aspergillosis (IPA) in hemato-oncological patients ranges from 4.7-13.1% [23]. Auberger et al. reported a breakthrough IFI incidence of 13% in hemato-oncological patients receiving posaconazole prophylaxis. All the IFIs were caused by organisms not belonging to the genus *Aspergillus*, and most were caused by filamentous fungi of the order *Mucorales* [24]. The study by Pang et al. recorded a breakthrough IFI incidence of 7.3% in hemato-oncological patients who in the absence of prior prophylaxis received antifungal treatment or targeted therapy with caspofungin. The proven breakthrough IFI rate due to *Aspergillus* spp. was established as 4.2% [25]. However, other studies have reported a lower and even zero incidence of breakthrough IFIs in high-risk hemato-oncological patients receiving azole prophylaxis [26].

Result of the survey: Nearly one-half of the specialists (47.8%) reported an incidence of breakthrough IFIs due to filamentous fungi (proven, probable and possible) in their Departments of 1-5%. The incidence was 6-10% according to 25.7% of the specialists. Thus, 73.5% of the participants estimated the incidence of breakthrough IFIs due to filamentous fungi in their centers to be 1-10%.

3. Which of the following risk factors for filamentous fungal infections do you consider to be most relevant in your patients?

Answers provided by the coordinators: a) Advanced age; b) Chronic obstructive pulmonary disease; c) The use of alemtuzumab; d) Chronic graft versus host disease under treatment; e) Iron overload.

Comment: Advanced age, iron overload, extensive chronic graft versus host disease (GVHD), and the use of monoclonal antibodies (alemtuzumab), as well as a poor general condition, are some of the main risk factors associated with the development of filamentous fungal infections in hematological patients [2]. A prospective epidemiological study of the SEIFEM has identified chronic obstructive pulmonary disease (COPD) as one of the main risk factors for IFI after the first chemotherapy cycle in patients with AML [27]. Iron overload and advanced age are described as key risk factors in hematopoietic stem cell transplantation (HSCT) and AML patients, respectively [28]. Another Spanish study based on a Delphi method and conducted by the Study Group of Risk Factors for IFI identified: a) a total of 18 key risk factors for IFI due to filamentous fungi in allotransplant patients, including acute grade III-IV and chronic extensive GVHD, as well as the use of anti-CD52 biological therapies (alemtuzumab); b) a total of 7 key risk factors in patients with acute leukemia or myelodysplastic syndrome, including azole prophylaxis; and c) a total of 5 key risk factors in patients with multiple myeloma or lymphoma, including the administration of anti-CD52 biological therapies. No consensus was reached in any of the three groups of hemato-oncological patients on considering advanced age, COPD or iron overload as key risk factors for IFI due to filamentous fungi [29]. The consensus document on the treatment of IFI due to filamentous fungi in hematological patients prepared by the Spanish Society of Chemotherapy (*Sociedad Española de Quimioterapia* [SEQ]) identifies the presence of intense neutropenia, cytomegalovirus infection, GVHD, and treatment with corticosteroids, anti-TNF-α agents or alemtuzumab as factors identifying high risk patients. In turn, older age (> 65 years), COPD and iron overload constitute risk factors for secondary IFIs in this population [3].

Result of the survey: In the opinion of 69.0% of the specialists, chronic GVHD under treatment is the main risk factor for filamentous fungal infections in hemato-oncological patients. On the other hand, advanced age would be the most important risk factor according to 16.3% of the participants; alemtuzumab use according to 8.5%; COPD according to 3.9%; and iron overload according to the remaining 2.3%.

Diagnosis

1. In the high-risk patient, indicate the situations in which you use the galactomannan test.

Answers provided by the coordinators: a) In starting early treatment; b) In confirming the suspected diagnosis and deciding the duration of treatment; c) I do not have this test in routine clinical practice; d) I use other biological markers of IFI; e) In the first two situations.

Comment: Early antifungal therapy leads to an improved prognosis in patients with invasive aspergillosis, and galactomannan antigen (GA) testing is a useful tool for the early diagnosis of IFI caused by *Aspergillus* spp. in neutropenic patients [1,30]. Although the specificity and sensitivity of the GA test varies considerably in the literature [31], the study by Maertens et al. shows a sensitivity of 92.5%, a specificity of 95.4% and positive and negative predictive values of 93% and 95%, respectively. The authors therefore recommend its routine use in screening neutropenic patients at risk for invasive aspergillosis [32]. The IDSA and ESCMID guides recommend the determination of GA in bronchoalveolar lavage as a precise marker for the diagnosis of invasive aspergillosis in both pediatric and adult hemato-oncological patients [33,34]. In contrast, the guides state that GA should not be used for routine blood screening in patients who have received antifungal prophylaxis or therapy. In this setting, serial plasma GA screening may be used in patients with elevated baseline GA titers in order to monitor disease progression and therapeutic response, and to establish the prognosis [33,34].

Result of the survey: A total of 61.7% of the participants claimed to use the galactomannan antigen test to start early treatment in the event of a positive result or to confirm suspected IFI and decide the duration of treatment. Likewise, 22.8% claimed to use the test only to start early treatment, while 11.0% only considered its use for confirming the diagnosis of IFI due to filamentous fungus and deciding the duration of treatment. On the other hand despite the availability of the galactomannan test, 2.3% of the specialists preferred to use other IFI biomarkers. Lastly, 2.2% of the specialists reported that the galactomannan test was not available in their Departments.

2. Which of the following techniques are available at your center in routine practice for the diagnosis of invasive aspergillosis? (Multiple answers are allowed).

Answers provided by the coordinators: a) β-D-Glucan; b) Galactomannan; c) Polymerase chain reaction (PCR); d) Lateral flow device (LFD); e) All of them.

Comment: The new diagnostic tools, mainly GA, (1 → 3) β-D-glucan and PCR-based techniques, have shown their usefulness in the early detection of IFIs in high-risk hematological patients, but their precision may be conditioned by the administration of antifungal prophylaxis [28]. In fact, prophylaxis with extended-spectrum azoles may reduce the sensitivity of the GA test by up to 30% [5]. The measurement of serum or plasma (1 → 3) β-D-glucan levels offers high precision in discriminating between patients with and without IFI, particularly those infections caused by *Candida* spp. or *Aspergillus* spp. [35,36]. Accordingly, the Infectious Diseases Society of America (IDSA) recommends the serum (1 → 3) β-D-glucan test for the diagnosis of invasive aspergillosis in hematooncological patients, though it emphasizes that the test is not specific for *Aspergillus* [33]. In this context, the study carried out by Lamoth et al. concluded that the GA and (1 → 3) β-D-glucan detection tests are complementary tools for the early diagnosis of invasive aspergillosis, and may play a role in monitoring treatment response in hemato-oncological patients. However, the authors underscore that none of these tests are appropriate for the detection of mucormycosis - the second most common cause of IFI in this population, with clinical manifestations that may be similar to those of aspergillosis [37]. The recording of two positive PCR-based test results affords 95% specificity and 64% sensitivity for the detection of IFI due to *Aspergillus* spp. [38]. Thus, standardized use of PCR in combination with GA may constitute an effective strategy for the early diagnosis and treatment of aspergillosis in the high risk population [39]. The detection of genetic markers associated with antifungal resistance further increments the benefits obtained [40,41]. In this regard, the IDSA and ESCMID guides recommend that the PCR test results should be evaluated together with those of other diagnostic tests, and within the clinical context of the patient [33,34]. Lateral flow technology (LFD) for *Aspergillus* is useful for the diagnosis of invasive aspergillosis in high-risk immunocompromised patients [42]. Combined with quantitative PCR (qPCR), LFD shows 100% sensitivity and 87.5% specificity in diagnosing invasive pulmonary aspergillosis in hemato-oncological patients [43].

Result of the survey: The responses provided by the professionals show the high availability (up to 95.6%) of the galactomannan test for the detection of IFI due to filamentous fungi in Spanish hospitals involved in the management of highrisk hemato-oncological patients. The availability rate is 41.6% in the case of the PCR test, versus 10.2% for the (1 → 3) β-D-glucan test, and only 0.7% for LFD testing. It should be mentioned that only four of the 137 consulted professionals (2.9%) had access in their centers to all four tests, i.e., galactomannan, PCR, (1 → 3) β-D-glucan and LFD.

Treatment

1. With regard to systemic antifungal therapy after extended-spectrum azole prophylaxis, which of the following options do you think is most reasonable?

Answers provided by the coordinators: a) Use such therapy according to a pre-emptive strategy; b) Use it according to an empirical strategy; c) Use it only in targeted therapy; d) The first two situations; e) Do not use such approach.

Comment: The consensus document generated under the auspices of SEQ recommends the administration of empirical antifungal treatment in the event of persistent fever, absence of clinical improvement and negative microbiological test results despite the administration of antibiotic therapy for more than three days (high-risk patients) or more than 5-7 days (intermediate-risk patients), and in all situations of significant clinical deterioration, regardless of the duration of fever. In turn, pre-emptive treatment should be provided in the case of positive GA test results or thoracic or paranasal sinus computed axial tomography (CAT) findings. Lastly, targeted therapy should be administered in the presence of an infectious focus and proven or probable IFI [3]. Pre-emptive therapy seeks to reduce the number of patients receiving empirical treatment and consequently avoid unnecessary exposure to antifungals, with a lowering of the healthcare costs [2]. However, the relatively low sensitivity of GA testing under certain circumstances, as in extended-spectrum azole prophylaxis [44], and sometimes the low specificity of the radiological techniques [3,45], make it necessary to start empirical treatment [46]. Therefore, and despite the risk of overtreatment, empirical therapy remains an appropriate antifungal strategy for high-risk patients receiving broad-spectrum antifungal prophylaxis [3,5,12,33,47]. As concluded by Ko et al., empirical therapy remains a reasonable and pragmatic approach to the threat posed by IFIs, especially in high-risk patients with moderate to severe disease or severely impaired immune function [48].

Result of the survey: Most of the consulted specialists (52.2%) considered that in the case of high-risk hematooncological patients who have received extended-spectrum azole prophylaxis, systemic antifungal treatment should be used

based on a pre-emptive and empirical strategy. In turn, 16.9% considered that antifungal treatment after prophylaxis should only be administered in the context of an empirical strategy, while 13.2% considered it indicated only as part of a pre-emptive management strategy. In contrast, while 14.0% of the participants stated that treatment should only be used based on a guided strategy, 5 of them (3.7%) did not consider systemic antifungal therapy to be indicated if the patient has received prophylaxis with an extended-spectrum azole.

2. In a patient with prolonged neutropenia after induction chemotherapy for AML, receiving posaconazole prophylaxis and presenting with fever, lung infiltration and positive serum galactomannan, which option do you think is most reasonable?

Answers provided by the coordinators: a) Do not make therapeutic changes, since it is probably a false positive result; b) Start treatment with an echinocandin; c) Given the possibility of poor absorption of posaconazole, switch to intravenous voriconazole; d) Start treatment with liposomal amphotericin; e) Given the possibility of poor absorption of oral posaconazole, switch to intravenous posaconazole.

Comment: The standardized use of prophylaxis in hemato-oncological patients has favored the emergence of resistant fungal pathogens such as *Candida* spp., *Cryptococcus* spp. and filamentous fungi including resistant species of *Aspergillus* [12,49]. Some authors suggest that continuing azole prophylaxis may be an option in the management of breakthrough filamentous fungal infection [50]. However, several studies have shown that the identified fungal pathogens exhibited resistance to the azoles previously administered on a prophylactic basis [12,23,51]. On the other hand, the possible presence of false positive results with the GA test reported in different situations should be considered in the case of treatment with specific antibiotics (usually piperacillin-tazobactam and amoxicillin-clavulanic acid), neonatal colonization with *Bifidobacterium*, and invasive fungal infections other than aspergillosis – including but not limited to penicilliosis, fusariosis, histoplasmosis and blastomycosis [52]. The efficacy of posaconazole prophylaxis in hemato-oncological patients at high risk of suffering IFIs may be limited by the variable absorption of posaconazole. It must be taken into account that many of these patients are being treated with proton pump inhibitors, which have been shown to cause inadequate absorption of this antifungal agent [24]. In this regard, various clinical practice guides and expert consensus documents and opinions [3,33,34], as well as the evidence found in the literature [12,45,53] support the switch in antifungal class. The consensus in this situation is to recommend liposomal amphotericin B, due to the high probability of breakthrough IFI secondary to prior antifungal failure [3].

Result of the survey: The vast majority of the healthcare professionals (83.3%) considered that therapy with liposomal amphotericin B should be started in AML patients receiving prophylaxis with oral posaconazole and who present with fever, pulmonary infiltration, and positive serum galactomannan. On the other hand, based on the possibility of poor absorption of the oral posaconazole formulation, 14.4% and 0.8% of the specialists respectively contemplated a switch to intravenous voriconazole or posaconazole in this situation. Lastly, while 1.5% of the participants claimed not to make any treatment modification and maintain prophylaxis with oral posaconazole, given the possibility of a false-positive result, none of the specialists would choose to start treatment with an echinocandin in this situation.

3. In patients with highrisk febrile neutropenia under prophylaxis with oral extended-spectrum azoles and failing to respond to 5 days of broad-spectrum antibiotics, what would you recommend?

Answers provided by the coordinators: a) Empirical antifungal treatment; b) Repeat culture and modify the broad-spectrum antibiotic treatment; c) Assess galactomannan and high-resolution pulmonary CAT; d) Wait a few days more, since antibiotics may take time to produce an effect; e) Switch azole.

Comment: As soon as breakthrough IFI is suspected, it should be evaluated whether the origin is related to failed prior antifungal therapy, the patient immune status, and/or the presence of a resistant fungus [21]. The sensitivity of filamentous fungus culture is usually poor, and is even lower in hemato-oncological patients due to the prior antifungal therapy provided [54]. Galactomannan antigen testing is a useful tool for the early diagnosis of IFI due to *Aspergillus* spp. in neutropenic patients, but its use for screening purposes in patients receiving prophylaxis is not advised [1,30]. On the other hand, systematic thoracic and paranasal sinus CAT evaluation in the presence of febrile neutropenia has improved the early diagnosis of pulmonary fungal infection and therefore the start of early treatment [55]. Accordingly, the SEQ recommends GA and/or thoracic and paranasal sinus CAT evaluation, with the administration of pre-emptive therapy if the findings prove positive [3]. In case of a negative GA test and extended-spectrum azole prophylaxis, there is a lesser risk of IFI due to *Aspergillus* spp. but not to other filamentous fungi, especially Mucorales [3]. In this context, the SEQ recommends the administration of empirical treatment in the event of persistent fever, absence of clinical improvement and negative microbiological test results despite the administration of antibiotic therapy for more than three days (high-risk patients) or more than 5-7 days (intermediate-risk patients), as well as in all situations where significant clinical deterioration of the patient is observed regardless of the duration of fever [3]. The IDSA and ESCMID clinical practice guides, as well as the SEQ consensus, recommend replacing prophylaxis in the form of broad-spectrum azoles with another class of antifungals in the case of suspected breakthrough IFI [3,33,34].

Result of the survey: In the case of high-risk hemato-oncological patients with febrile neutropenia receiving oral extended-spectrum azole prophylaxis and in whom no response is observed after 5 days of treatment with broad-spectrum

antibiotics, most of the consulted professionals (57.9%) considered it necessary to wait for the results of the GA test and/or the high-resolution thoracic CT report before making any therapeutic decision. On the other hand, 35.8% of the specialists would start empirical antifungal treatment; 3.2% would postpone any decision for a few days pending response to antibiotic treatment; 2.4% would repeat cultures and modify broadspectrum antibiotic therapy; and the remaining 0.7% would switch azole.

4. In patients with high-risk febrile neutropenia under prophylaxis with oral extended-spectrum azoles and failing to respond to 5 days of broad-spectrum antibiotics, if an empirical antifungal is decided, which drug would you choose?

Answers provided by the coordinators: a) Intravenous voriconazole; b) intravenous posaconazole; c) Caspofungin; d) Anidulafungin; e) Liposomal amphotericin B.

Comment: Empirical therapy in hemato-oncological patients should be started as soon as possible and should offer broad-spectrum antifungal activity [3,5,12,45]. The SEQ consensus document states that while posaconazole is effective against some Mucorales, effective plasma concentrations are often not reached, and that voriconazole exerts no activity against Mucorales. For this reason, liposomal amphotericin B is recommended because of its broad spectrum of antifungal activity, covering *Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., *Fusarium* spp., and *Mucor* spp. [3]. Caspofungin has been used for the empirical treatment of invasive fungal infections, with a good safety profile [56,57]. The efficacy of posaconazole prophylaxis in hemato-oncological patients at high risk of suffering IFIs may be limited by the variable absorption of posaconazole. It must be taken into account that many of these patients are being treated with proton pump inhibitors, which have been shown to cause inadequate absorption of this antifungal agent [24].

Result of the survey: The vast majority of the specialists (77.6%) considered that if empirical antifungal treatment is decided in high-risk hemato-oncological patients with febrile neutropenia receiving oral extended-spectrum azole prophylaxis and in whom no response is seen after 5 days of broad-spectrum antibiotic therapy, the drug of choice should be liposomal amphotericin B. The antifungal agent chosen in this situation would be caspofungin according to 10.5% of the consulted specialists; intravenous voriconazole according to 7.5%; anidulafungin according to 2.2%; and intravenous posaconazole according to the remaining 2.2%.

CONCLUSIONS

To the best of our knowledge, this study constitutes the first national survey on the management of IFIs due to filamentous fungi in Spain. The survey offers a good view of the problem posed by IFIs among physicians involved in the care of high-risk hemato-oncological patients. Based on the results obtained, we can conclude the following: 1) A total of 75.3% of the participants estimate the incidence of breakthrough IFI due to filamentous fungus in their Departments as being 1-10%. 2) A total of 83.3% of the participants decide a change in antifungal class after failure of prophylaxis, in concordance with the recommendations of the national consensus documents.

ACKNOWLEDGEMENTS

Gilead Sciences provided financial support for data acquisition, statistical analyses and medical writing, with no influence in the content.

CONFLICTS OF INTEREST

CV has been a consultant to and received lecture fees from Astellas Pharma, Gilead Siences SL, Merck Sharp and Dohme, and Pfizer

JF has been a consultant to and received lecture fees from Astellas Pharma, Gilead Sciences SL, Merck Sharp and Dohme, and Pfizer.

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