The management of febrile neutropenia in the posaconazole era: a new challenge?

Livio Pagano,[1] Morena Caira[1] and Manuel Cuenca-Estrella[2]

[1]Istituto di Ematologia, Università Cattolica del S.Cuore, Rome, Italy; [2]Servicio de Micología, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain

E-mail: lpagano@rm.unicatt.it *doi:10.3324/haematol.2012.062166*

Over the years, the spectrum of patients at risk for invasive fungal disease (IFDs) has expanded. This is a result of the aging of the general population, progress in supportive care allowing clinicians to perform a higher number of aggressive and curative treatments, the introduction of new drugs in clinical practice (i.e. monoclonal antibodies, TNF-inhibitors), and the increasing number of transplant procedures.[1-3] However, hematologic patients, and in particular those suffering from acute myeloid leukemia (AML) and those treated with allogeneic stem cell transplant (allo-HSCT), still make up the biggest proportion of cases. Given the high mortality rate for IFDs, the use of mold active prophylaxis has increased in recent years, particularly in AML patients.

It is well known that a hypothetical *ideal* prophylactic agent should combine favorable profiles in terms of efficacy, spectrum, toxicity, cost, interactions and resistance generation. Two randomized clinical trials (RCT) demonstrated that fluconazole reduced the incidence of candidiasis in allo-HSCT when compared to placebo.[4,5] However, its lack of activity against molds significantly limits the benefit of its use. Itraconazole covers a wider range of fungi, but the use of this drug was limited by poor absorption of the capsules and side effects from the oral solution.[6,7]

Posaconazole appears to be a valid alternative to old triazoles as it offers both a wide spectrum of activity and an acceptable toxicity profile. Two RCTs showed posaconazole to be more efficacious and to have an excellent safety profile in high-risk patients; both studies reported a significant reduction in breakthrough IFDs in a high-risk population[8,9] and in antifungal use. Interestingly, among AML patients, posaconazole prophylaxis was shown also to have a significant impact on overall survival.[8] However, it is worth noting that the impact of posaconazole on overall survival has never been proved by multivariate analysis. This is important given that both the phase and extent of the hematologic malignancy play a crucial role in determining patient outcome.[10]

These recent data led to the approval of posaconazole prophylaxis in high-risk categories, and all current consensus guidelines recommend this approach with a high level of evidence.[11-13]

Consequently, the use of posaconazole in hematology departments is on the increase. In this context, *real life* experiences may be of help in assessing whether good results from RCTs can be translated into clinical practice.[14-21] All these experiences mainly focus on acute myeloid leukemia patients. As shown in Table 1, all reported experiences agree on the advantages of posaconazole in terms of proven/probable IFD incidence.

However, impressive results with posaconazole from RCTs should not lead physicians to the dangerous belief that IFDs are no longer a problem. It is worth noting that, despite the higher efficacy and the wider spectrum of this prophylactic agent, breakthrough infections may still occur, even if these are more rare. This is particularly true in clinical contexts other than clinical trials in which unselected, high-risk patients are treated and analyzed (Table 1). The physician must identify IFD cases as soon as possible in order to guarantee early and adequate treatment to patients.[22]

Physicians are now, therefore, faced with the question of how to manage febrile neutropenia in patients receiving posaconazole prophylaxis.

Given that clinical success depends on the achievement of adequate serum levels of the drug, controling compliance with oral drug intake is expected to be the first step in a management algorithm; signs and symptoms of diarrhea and gastrointestinal graft-*versus*-host disease (GVHD) should also be investigated. Determining serum posaconazole concentration would probably be the best and most direct way to answer these questions but most centers do not make this routine practice.[23] However, it is worth noting that *in vitro* experiments have demonstrated that the concentration of posaconazole in mammalian host cell membranes may represent a new mechanism to mediate drug efficacy. This may help reinterpret the discrepancies between serum antifungal levels and efficacy.[24]

Maertens and colleagues first showed that the incorporation of new techniques into a diagnostic algorithm led to antifungal treatments being halved.[25] Since then, there has been much debate about whether an empirical or a pre-emptive approach should be first choice in hematologic patients.[26-31] All proposed pre-emptive approaches strictly rely on newer diagnostic procedures approved for clinical use (galactomannan, CT-scan, (1-3)β-D-glucan) and on polymerase chain

Table 1. Incidence of proven/probable invasive fungal diseases in acute myeloid leukemia after posaconazole prophylaxis: data from different types of study.

References	Years	Type of study	N. pts	N. proven/probable breakthrough IFDs	Incidence %
RCT					
Cornelly *et al.*,[8]	2002-05	RCT	304	7	2%
"Real life" studies					
Michallet *et al.*[19]	2007-08	Pros	55	2	3.6%
Candoni *et al.*[15]	2009-10	Retro	55	2	4%
Lerolle *et al.*[18]	2007-10	Retro	209	8	3.8%
Egerer *et al.*[16]	2007-09	Retro	76*	1	1.3%
Vehreschild *et al.*[20]	2006-08	Retro	77	3	3.9%
Hahn *et al.*[17]	2007-08	Retro	21	1	5%
Busca *et al.*[14]	2009-10	Retro	61	0	0
Ananda-Rajah *et al.*[13]	2006-10	Retro	68	0	0

*RCT: randomized clinical trial; Retro: retrospective study; Pros: prospective study; IFDs: invasive fungal diseases. * number of chemotherapy courses.*

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reaction (PCR)-based techniques which are still under clinical investigation. However, many doubts have been raised about the reliability of diagnostic tools in the new and unexplored context of highly active anti-mold prophylaxis.

In particular, sensitivity of the galactomannan assay has been reported to be highly variable.[32] It is well-known that galactomannan is released from the cell wall during hyphae growth and that antigen serum levels strongly correlate with fungal burden. It has been demonstrated in an animal model that posaconazole prophylaxis decreases circulating galactomannan indices.[33] Marr and colleagues confirmed this in a clinical context, reporting that prior administration of mold-active antifungal drug decreases galactomannan test sensitivity by 30%.[34] Its reduced accuracy in hematologic patients receiving itraconazole, posaconazole or voriconazole prophylaxis could be a significant limitation to the use of galactomannan quantification as a screening technique. Timing of antifungal therapy has been shown to have a major impact on hospital mortality and reduced sensitivity, and a lower negative predictive value could lead to treatment being delayed.

It is also worth noting that the performance of a diagnostic test is largely influenced by the baseline prevalence of infections in the target population. Consequently, since posaconazole seems to reduce the incidence of IFDs, the positive predictive value of diagnostic tools is also expected to decrease. Notably, current ECIL guidelines suggest the use of monitoring for galactomannan in neutropenic patients who have a relatively high *a priori* probability (5-10%) of developing IA.[35]

Other authors have recently used an animal model to explore the possible influence of antifungal drugs on both galactomannan and quantitative PCR-based assays. It was found that the use of posaconazole in either prophylaxis or treatment may reduce the value of a negative PCR result in the early phase of aspergillosis, resulting in the need for daily PCR-based determinations for the first week.[36] In the same experience, posaconazole treatment also resulted in a delay in galactomannan positivity. In this context, frequent and early testing appears to be needed to optimize diagnostic procedures, with the burden of additional costs in terms of economical and human resources.

Therefore, the optimal management of febrile neutropenia after posaconazole remains an unanswered question. A pre-emptive approach should be used with caution in this new clinical context. Despite the risk of overtreatment, empirical therapy still appears to be a valid and safe antifungal approach, particularly in the context of a wide spectrum anti-mold prophylaxis. Newer diagnostic tools have been shown to be reliable and accurate methods for the early detection of fungal diseases when serial determinations are performed in high-risk hematologic patients but the influence of mold-active prophylaxis on their accuracy should be noted. Further confirmation of the validity of diagnostic procedures is needed in this clinical setting to understand how best to use them. In addition, use of new detection techniques, such as quantification of fungal components in respiratory samples, should also be the subject of further analysis.

Livio Pagano is Associated Professor of Hematology at the Catholic University of Sacred Heart, Rome, Italy. He is past-president of Federazione Italiana di Micologia Medica ed Animale (FIMUA) and executive member of EORTC Infectious Diseases Group. His main areas of interest are diagnosis and treatment of hematologic malignancies, clinical and epidemiology of secondary leukemias, and the management of infectious complications in neutropenic patients.

Morena Caira is a post-doctorate reserch fellow in hematology at the Catholic University in Rome, Italy. Her major research interests include the epidemiology, diagnosis and treatment of infections in immunocompromised patients.

Manuel Cuenca Estrella is the Director of the Spanish National Center for Microbiology and the Scientific Director of the Spanish Reference Laboratory of Medical Mycology where he runs a variety of research projects and scientific activities focused on fungal infections in man. He is the former Chairman of the European Fungal Infections Study Group of the European Society of Clinical Microbiology and Infectious Diseases (EFISG-ESCMID), a member of the Steering Committee of the Antifungal Subcommittee of Antifungal Susceptibility Testing of the European Committee of Antimicrobial Susceptibility Testing (AFST-EUCAST), and a member of other international societies and study groups.

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