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Joanna Lumb, medical writer, London, UK

Unmet needs in managing invasive fungal infections in haemato-oncology patients

Invasive fungal infections (IFIs) remain an important cause of morbidity and mortality in haemato-oncology patients. The challenges of diagnosis, new fungal species and the best approach to using antifungal drugs were among major topics discussed in a series of oral and poster presentations at the 38th annual meeting of the European Group for Blood and Marrow Transplantation in Geneva, Switzerland.

Importance of knowing local fungal epidemiology

Current diagnostic tools for IFI are insufficient and treatment decisions are often made without knowing which fungus is causing the disease. This means it is important to consider the local epidemiology of fungal pathogens to devise local management protocols.

Paul Verweij (Professor of Medical Microbiology, Radboud University Nijmegen Medical Centre, The Netherlands) noted that the taxonomy of the *Aspergillus fumigatus* complex has changed. Using DNA sequencing, 30 new sibling species, such as *A. lentulus* and *A. udagawae*, have been identified within the group that used to be called *A. fumigatus*. In the US TRANSNET study, 5% of invasive aspergillosis infections that would have previously been identified as *A. fumigatus* were actually caused by these sibling species. This altered epidemiology is probably clinically relevant as the new species appear to be less susceptible than *A. fumigatus* to azole antifungal agents.

Other moulds, such as *Zygomycetes*, also have to be considered. Professor Verweij explained that there is some evidence of an increase in invasive zygomycosis. Treatment options for this infection are limited: polyenes are effective as first-line treatment and posaconazole also has activity.

Although azole resistance in *Aspergillus* is still quite low, this is another issue that will become important, Professor Verweij said. He emphasised that knowledge of local drug resistance is essential for selecting antifungal therapy. A recent study in The Netherlands

showed an overall 5.3% prevalence of itraconazole resistance in isolates of *A. fumigatus*, with 90% of this resistance due to TR/L98H mutation in the CYP51A gene, a mechanism thought to be associated with environmental use of azoles. Of these resistant strains, 80% were also resistant to voriconazole and 17% to posaconazole.[1] The TR/L98H resistance mechanism has also been found in other European countries, and new data suggest that the isolates have a common ancestor, indicating that this resistance is spreading and likely to become more prevalent.

Prophylaxis, pre-emptive or empirical therapy?

Antonio Pagliuca (Professor of Stem Cell Transplantation at King's College Hospital, London, UK) commented that fungal diagnostic strategies are still in their infancy. At present, only 25% of patients with *Aspergillus* infection are diagnosed pre-mortem. And aspergillosis-related mortality in allogeneic haematopoietic stem cell transplantation (HSCT) remains high, with US data for 2010 showing that over 50% of patients who develop *Aspergillus* infection will die from it.

A key question for clinicians is which approach to take for using antifungal drugs: prophylactic, pre-emptive (diagnostic-driven) or empirical (fever-driven) therapy.

Professor Pagliuca said that decisions on primary prophylaxis of IFIs should be made in the light of local epidemiology: if a centre has an *Aspergillus* infection rate of 10-15%, prophylaxis with a mould-active azole should be considered, bearing in mind that fungal infection can prejudice outcome of the next cycle of cancer therapy.

He said that the benefit of prophylaxis with posaconazole was shown in two key randomised trials.[2,3] More recently, a study comparing two other mould active agents, voriconazole and itraconazole, showed no statistically significant difference in incidence of infection or survival, though voriconazole was better tolerated.[4] Another study compared fluconazole (which does not have mould activity) and voriconazole[5] and showed no survival difference at six months, but Professor Pagliuca suggested that the use of routine galactomannan (GM) monitoring might have influenced outcome in this trial. He also noted that recent analysis of data from one centre had shown the superiority of mould-active agents for prophylaxis.[6]

There has been no direct comparison of posaconazole and voriconazole in IFI prophylaxis. However, a mixed treatment comparison of randomised controlled trials of prophylactic azoles in allogeneic haematopoietic cell transplant recipients was reported to the EBMT conference.[7] This systematic review, carried out by researchers in Europe, Australia, US

and Canada, included three open-label and two double-blind randomised trials involving 2147 patients. It suggested that mould-active azoles are more effective than fluconazole for preventing overall IFI incidence in this setting. There was no clear distinction between itraconazole, posaconazole and voriconazole. The researchers commented that until further data on comparative efficacy are available, other factors such as long-term tolerability, cost and ease of use may help in choosing the most appropriate azole for IFI prophylaxis.

Professor Pagliuca, who had contributed to this analysis, suggested that there is no longer a place for fluconazole prophylaxis.

The revised EORTC/MSG definitions of invasive fungal disease (IFD) are used as a diagnostic tool in clinical trials but there are few data on their usefulness in day to day practice. The King's Prospective Aspergillosis Study, reported to the conference by Mansour Ceesay *et al*,[8] was a prospective cohort study designed to evaluate "real world" incidence and outcome of IFD in patients undergoing HSCT or high-dose chemotherapy using all EORTC/MSG diagnostic tools. The study involved 203 patients, with minimum follow up of 4 months. It showed that using GM monitoring (plus CT scans) without beta-D-glucan testing would have underestimated the true incidence of infection by 9%, highlighting the need for a multidiagnostic approach. Dr Ceesay commented that the beta-D-glucan assay is technically difficult and expensive but that availability of this test is important in high-risk patients to avoid missing some cases.

Early treatment strategy

Discussing early treatment strategies for IFI, Professor Catherine Cordonnier (Hôpital Henri Mondor, Créteil, France) said that while there is consensus on the objectives of pre-emptive therapy (for example, to target high-risk patients, and to reduce administration of antifungal agents) there is no consensus on the clinical, biomarker and imaging criteria for starting antifungal therapy using this strategy. A safe pre-emptive approach has not yet been defined and two studies — the PREVERT open label randomised trial[9] and the HEMA e-Chart observational study[10] both found more fungal infection in the pre-emptive arm than the empirical treatment arm.

Professor Cordonnier noted that the EORTC 65091 study comparing pre-emptive and empirical therapy in haemato-oncology patients has recently started.

Referring to the use of serum GM testing as part of a pre-emptive strategy for early detection of IFD, Professor Verweij emphasized the importance of repeated testing, starting early. It is essential not to wait until a patient is thought to have infection.

Empirical antifungal therapy is still used in the vast majority of patients, especially in high-risk patients. A survey among a symposium audience showed that 77% of clinicians would use empirical treatment while 23% favoured a pre-emptive strategy.

Cause of death in allogeneic HSCT

Infections, notably those caused by moulds, remain a leading cause of death in the allogeneic HSCT setting. János Sinkó *et al* (St István & St László Hospital, Budapest, Hungary) reported an update of an autopsy-driven survey investigating infection-related deaths.[11] The single-centre retrospective survey compared data on fatal mould infections in patients undergoing HSCT between 2008-10 with data from a similar survey in 2003-6. There were no statistically significant differences in the two study periods, but the incidence of fatal invasive aspergillosis slightly decreased while deaths from mucormycosis showed a slight increase. Fatal aspergillosis occurred significantly earlier post-transplant than fatal mucormycosis.

Challenges in paediatric haematology

Some of the specific challenges in paediatric haematology patients were described by Dr Susana Rives (Hospital Sant Joan de Déu, Barcelona, Spain). Diagnostic tools are less reliable in the paediatric population: conflicting results have been reported on the predictive value of the serum GM test in children, and imaging techniques are also less informative — the typical CT signs of IFIs, such as halos or air crescents, are rare. Another issue is that triazoles should not be given concurrently with vincristine, one of the main components of acute lymphoblastic leukaemia treatment, because of neurotoxicity. Dr Rives said that her centre is currently undertaking a phase 2 study of nebulised amphotericin lipid complex as an approach to prophylaxis in children with acute leukaemia.

Viral and bacterial infections also important

Fungal infections are of course not the only infection risk in patients with haematological malignancies. Professor Vincent Emery (University College London, UK) noted that cytomegalovirus is an important cause of morbidity after allogeneic HSCT. Prophylaxis with anti-CMV drugs is not routine and pre-emptive treatment is generally used. Dr Martin Llewelyn (Brighton and Sussex Medical School, UK) pointed out that *Clostridium difficile* is

one of many causes of diarrhoea after HSCT and that this infection can be difficult to diagnose because presentation may be attenuated in neutropenic patients. Dr Llewelyn observed that the epidemiology of *C. difficile* in Europe has changed in the past 10 years: it has become more common and more severe, with these changes linked to new hypervirulent strains.

References

1. Van der Linden JWM, Snelders E, Kampinga GA, et al. Clinical implications of azole resistance in *Aspergillus fumigatus*, the Netherlands, 2007–2009. *Emerg Infect Dis* 2011;17:1846-54.

2. Cornely OA, Maertens J, Winston DJ et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007;356:348-59.

3. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007;356:335-47.

4. Marks DI, Pagliuca A, Kibbler CC, et al. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol* 2011;155:318-27.

5. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood* 2010;116:5111-8.

6. Ananda-Rajah MR, Grigg A, Downey MT, et al. Comparative clinical effectiveness of prophylactic voriconazole/posaconazole to fluconazole/itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. *Haematologica* 2012;97:459-63.

7. Bow E, Vanness D, Cordonnier C, et al. Primary prophylaxis of invasive fungal disease in allogeneic haematopoietic cell transplant recipients — a mixed treatment comparison of randomised clinical trials. *Bone Marrow Transpl* 2012;47:Suppl 1 (O354).

8. Ceesay MM, Berry L, Desai SR, et al. A comprehensive diagnostic approach improves the diagnostic accuracy of invasive fungal disease in adult haemato-oncology patients undergoing HSCT or high-dose chemotherapy – results of the King's Prospective Aspergillosis Study. *Bone Marrow Transpl* 2012;47:Suppl 1 (P465).

9. Cordonnier C, Pautas C, Maury S, et al. Empirical versus pre-emptive antifungal therapy for high-risk, febrile, neutropenic patients: A randomized, controlled trial. *Clin Infect Dis* 2009;48:1042-51.

10. Pagano L, Caira M, Nosari A, et al. The use and efficacy of empirical versus pre-emptive therapy in the management of fungal infections: the HEMA e-Chart Project. *Haematologica* 2011;96:1366-70.

11. Sinkó J, Csomor J, Barta A, et al. Infection-related deaths in the haematopoietic stem cell transplant setting. *Bone Marrow Transpl* 2012;47:Suppl 1 (P472).