New European leukaemia guidelines on antifungal prophylaxis

Antifungal prophylaxis should be a routine part of the supportive care for leukaemia patients undergoing chemotherapy and for other cancer patients who require allogeneic haematopoietic stem cell transplantation (HSCT), according to new European guidelines, produced by the 1st European Conference on Infections in Leukaemia (ECIL).

For induction chemotherapy of acute leukaemia, the guidelines give the strongest (level AI) recommendation to the antifungal agent, posaconazole 200mg tid, with level CI recommendations for fluconazole 50-400mg qd, and itraconazole 2.5mg/kg bid.

For allogeneic HSCT, ECIL has made AI recommendations for posaconazole 200mg tid and fluconazole 400mg qd, and a BI recommendation for itraconazole 200mg bid. Micafungin 50mg qd received a CI recommendation.

Presenting the new guidelines, Dr Johan Maertens, Head of Clinical Haematology, at the University Hospital Gasthuisberg, Leuven, Belgium, explained that, while prophylactic antifungal treatment is already widely used in leukaemia and HSCT patients, evidence-based recommendations were needed for the most appropriate agents.

‘Almost 60 clinical trials with over 7000 patients had been carried out, but solid scientific conclusions were not available because of the variation in design, power and endpoints of the studies. There were also new agents which needed to be considered,’ said Dr Maertens.
He added that the decision to prioritise posaconazole for antifungal prophylaxis was based on the recent publication of two large clinical trials which demonstrated the benefits of the drug in preventing invasive aspergillosis and reducing deaths related to invasive fungal infections [1, 2].

In one of the studies, in over 600 patients with acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS), posaconazole also significantly reduced overall mortality compared with either fluconazole or itraconazole (p=0.04) [2].

‘This is the first large well controlled study in this setting which has shown a reduction in overall mortality,’ pointed out lead investigator of the study, Dr Oliver Cornely, from the Department of Internal Medicine at the University of Cologne, Germany.

He added that the study showed that the number needed to treat (NNT) for posaconazole to prevent a fungal infection in neutropenic patients was 14 – low enough for physicians to see benefits in their practices.

Dr Cornely also reported data from his own unit in Cologne which showed a reduction in probable or proven invasive fungal infection during the first induction cycle of chemotherapy from 15% in the years 2003-2005, before antifungal prophylaxis was introduced, to only 3% - just one patient – in 2006, following the introduction of posaconazole prophylaxis for AML patients.

**Empirical or pre-emptive therapy?**

Pre-emptive anti-fungal therapy based on early diagnostic evidence of fungal invasion could reduce the need for empirical treatment in some cancer and other high-risk patients. But, as Professor John Perfect, from the Department of Molecular Genetics and Microbiology at Duke University Medical Centre,
Durham, USA, pointed out at a symposium sponsored by Schering-Plough/Essex Pharma, few centres are routinely using tests to detect fungal infections before the onset of clinical symptoms, owing to doubts about the accuracy and/or interpretation of results, and expense.

He suggested that, when combined with CT scans for infiltrates, detection of the *Aspergillus* galactomannan antigen can be very effective in determining the need for pre-emptive therapy. He described a screening study of these techniques which showed that it was possible to reduce empirical antifungal use from 35% to 7.7% of treatment episodes, with an accompanying 63.6% survival rate for patients with invasive fungal infection (IFI) [3]. This approach also led to early initiation of antifungal therapy in 10 episodes where fungal infection was not suspected. Only one case of fungal infection – a patient with zygomycosis – was missed.

However, as Professor Perfect pointed out, there are only a few dozen places where galactomannan testing is available and, even in these hospitals, it is greatly underused. Other tests, such as β-D-glucan, which can detect infection 4-8 days before culture tests, and fungal DNA detection by polymerase chain reaction (PCR) techniques, are also promising, he said, but are not yet ready for routine practice.

Professor Perfect stressed that, in the meantime, it is essential that hospitals become more aware of their own fungal epidemiology and define high-risk groups who most need prophylaxis (e.g.: leukaemia patients undergoing chemotherapy, bone marrow, lung, pancreas and small bowel transplant patients, neonates, AIDS and ICU patients). He added than any analysis of the costs of antifungal prophylaxis should take account not only of the drug acquisition costs, but of the hospitalisation costs for patients with IFIs, currently estimated at over $82,000 per case for invasive aspergillosis and $34,000-$44,500 per patient for invasive candidiasis.
Could combination anti-fungal treatment improve outcomes?

Combining azoles or liposomal amphotericin B with echinocandins, or boosting the effects of conventional antifungal therapies with cytokines or novel antibodies, were proposed as possible new ways of improving future outcomes for patients with IFIs.

Speaking at a Gilead-sponsored symposium, Dr Luis Ostrosky-Zeichner, from the University of Texas, Houston, USA, described the results of the recent Combistrat Trial which reported that, at week 12, 80% of 15 immunocompromised patients with invasive aspergillosis treated with standard doses of liposomal amphotericin B (3mg/kg/d) and caspofungin had a favourable response, compared to 67% of 15 patients who had high-dose liposomal amphotericin B high dose (10 mg/kg/d).

Dr Ostrosky-Zeichner told delegates that this was the first prospective randomised trial of combination versus single agent therapy for invasive aspergillosis, and it will now be followed up with a larger study to try to confirm the results.

Building on the potential of combination therapy with newer antifungal agents, at the Novartis-sponsored symposium on biological treatments for fungal infections, Professor Malcolm Richardson, from the University of Helsinki, Finland, explained that combining antifungal agents with different modes of action and ranges of activity offers the potential to improve antifungal efficacy, shorten duration of therapy, lower drug-related toxicities and reduce the risk of resistance.

In this context, Professor Peter Pappas, from the Division of Infectious Diseases at the University of Alabama, Birmingham, USA, described *in vivo* and *in vitro* studies demonstrating the additive effects of granulocyte-macrophage colony stimulating factor (GM-CSF) on antifungal agents, but expressed concerns that
the cytokine could potentially aggravate the inflammatory response. Interferon-gamma has demonstrated synergy with antifungals *in vivo* and *in vitro*, he said, but data with these combinations against human fungal infections are limited.

Reporting the latest findings with the anti-candidal heat shock protein (HSP 90) antibody fragment, efungumab, Professor James Burnie, from the Department of Medical Microbiology at Manchester University, UK, showed early superiority of the combination of liposomal amphotericin B and efungumab compared to liposomal amphotericin B alone in the treatment of invasive candidiasis [4]. Eighty four per cent of 56 patients in the combination treatment group achieved a complete (clinical and mycological) response, compared to 48% of 61 patients in the amphotericin B group (P<0.001). Candida mortality at day 33 was 4% with combination treatment, compared to 18% with amphotericin B, and three month overall survival for the two treatments was the same, at 48%.

Professor Burnie explained that, for the future it would be important to identify patients most likely to benefit from the combined antibody/antifungal drug treatment, possibly based on their HLA and Toll-like receptor (TLR) haplotypes. *NeuTec Pharma* – the company which developed efungumab – has been acquired by Novartis and, in response to delegates’ questions, Professor Burnie predicted that issues related to the manufacture of the antibody raised by the European Medicines Agency (EMEA) would now be resolved.

**Emerging groups at risk of fungal infection**

Rheumatoid arthritis and colitis patients are amongst the new groups who are potentially at risk of fungal infection, as a result of treatment with the new generation of immunomodulatory agents, such as the anti-TNF antibodies, infliximab and etanercept.

In a wide ranging review, Dr Patricia Muñoz, from the Clinical Microbiology and Infectious Diseases Service, Hospital General Universitario Gregorio Maranon,
Madrid, Spain, reported FDA data (1998-2002) showing a fungal infection rate of 239/100,000 with infliximab and 70/100,000 with etanercept. She explained that the higher rate and earlier onset of infection (typically after about 40 days of treatment compared to 236 days) with infliximab was thought to be due to the more complete binding of the antibody to the cytokine.

Dr Muñoz also described the different profiles of the monoclonal antibodies, rituximab and alemtuzumab, which cause lysis of B lymphocytes, and are licensed for lymphoma treatment. While rituximab appears to be associated mainly with viral infection, a significant proportion of serious fungal infections have been reported with alemtuzumab. Dr Muñoz explained that growing evidence suggests that patients treated with alemtuzumab to combat transplant rejection are most at risk of fungal infection, and she suggested that antifungal prophylaxis should be considered for these patients and for those requiring alemtuzumab for long-term cancer treatment of two years duration, and more.

**The role of fungi in asthma: a new indication for anti-fungal therapy?**
Antifungal treatment may have a role to play in the treatment of asthma, according to new data from the FAST study, presented by Professor David Denning, from the Wythenshawe Hospital, Manchester, UK, in his keynote lecture on new clinical and molecular targets for antifungal therapy.

Patients with severe asthma and proven fungal sensitivity scored significantly better on the well respected Asthma Quality of Life Questionnaire (AQLQ) after eight months treatment with itraconazole, in addition to their usual medication, than placebo (p=0.014). Professor Denning explained that the 0.82 improvement in AQLQ score achieved with itraconazole was well above the 0.5 threshold generally agreed to have clinical significance, and was higher than the 0.4 improvement seen with the recently introduced, novel antibody treatment for severe asthma, omalizumab.
References