

16th Congress of Clinical Microbiology and Infectious Diseases

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Report by Vicki Madden, Medical Writer

Introduction

More than 6000 delegates met in Nice, France, to hear international experts discuss clinical research and public health problems that affect the care of patients both in hospital and in the community. Some of the important topics raised at the Congress included antibiotic resistance, avian flu, emerging viral infections, tuberculosis, MRSA and antifungal therapies.

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in patients who are immunocompromised or immunosuppressed. As more and more people are either recipients of transplants or are neutropenic after receiving cancer treatment, the incidence of fungal infections are increasing and so effective antifungal therapy has become an essential part of successful case management.

Much of the discussion at the antifungal presentations in Nice centered on how and when to treat patients at high risk of fungal infections. Early diagnosis of IFIs is critical to improving patient outcome, but difficulties in diagnosing the fungal infection early have meant that many high-risk patients with persistent fevers have been treated empirically, prompted by a lack of response to broad-spectrum antibacterial therapy. Whilst this approach ensures that many patients are treated for suspected fungal infections, very few patients may actually experience full benefit at significant potential toxicity and cost. Less than optimal doses of toxic antifungal agents may be used, favouring the emergence of more resistant organisms.

Concerns about when to initiate antifungal therapy were reflected in several oral

sessions and symposia. These focused on advances in the diagnosis of fungal infections and when to employ prophylactic or pre-emptive treatment in patients most at risk of developing IFIs.

Details of two large trials that studied the prophylactic use of the broad-spectrum triazole posaconazole (Noxafil® Oral Suspension, Schering-Plough Corporation) were also discussed at the ECCMID congress. These showed that posaconazole could reduce the incidence of IFIs as well as reduce the overall mortality in high-risk patients. These results have underlined the need to revise the 1st European Conference on Infections in Leukemia (ECIL) recommendations. These state that none of the antifungal agents which were available when the guidelines were developed can be used in high-risk patients with acute leukaemia or in recipients of stem cell transplants.

This report focuses specifically on the treatment options and strategies for caring for patients at risk of developing an invasive fungal infection.

Increasing incidence of fungal infections in high risk patients

IFIs are a major cause of morbidity and mortality in patients with hematological malignancies who are susceptible to infection following myelosuppressive chemotherapy, resulting in neutropenia. Graft failure and graft versus host disease (GVHD), as well as the immunosuppression required for GVHD management can also exacerbate susceptibility to IFIs in hematopoietic stem cell transplant (HSCT) recipients.

Speaking at a Schering-Plough sponsored symposium, 'Tailoring initial therapy according to epidemiologic trends', Dr Christopher Kibbler, Royal Free Hospital, London, England, said that in recent years there had been a steady increase in the incidence of IFIs. 'Although the incidence of invasive moulds is lower than that of *Candida* species, aspergillosis remains the big killer,' he said. 'Mortality rates for high-risk patients are around 26% for invasive candidiasis, whilst in

HSCT recipients mortality rates of 87% for invasive aspergillosis have been reported.' He added that the vast majority of moulds seen were aspergillosis species, although since the 1990s there has been a rise in the incidence of zygomycosis and fusariosis. 'In HSCT recipients and patients with hematological malignancies, mortality rates as high as 91% have been reported with infections due to zygomycetes and at least 70% with *Fusarium* species.'

Risk factors

Speaking at another symposium, Professor Thierry Calandra, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, outlined the main risk factors for IFIs. 'Invasive fungal infections are an important cause of mortality and it is therefore vital to identify those patients who are at greatest risk. High-risk patients include cancer patients with prolonged and profound neutropenia following chemotherapy or HSCT. Patients are also at risk if they have had prolonged steroid therapy or antibiotics for e.g. pneumonia.'

Professor Calandra added that risk factors for candidiasis include:

- Underlying disease
- Chemotherapy
- Mucositis
- Profound neutropenia of long duration
- Candida colonisation at more than one site
- IV catheterisation
- Total potential nutrition
- Antibiotic therapy
- Renal therapy
- No antifungal prophylaxis

Risk factors for invasive aspergillosis include:

- Underlying disease
- Graft versus host disease

- Steroid therapy
- Increasing age
- Renal failure
- Lack of antifungal prophylaxis

Prophylactic treatment with posaconazole

The importance of early treatment was emphasised by Professor Johann Maertens, University Hospital Gasthuisberg (Leuven), Belgium, who said that studies now show that if treatment is started before confirmation of a fungal infection, survival rates can be improved. Professor Maertens was presenting the efficacy and safety results of two clinical trials where posaconazole was used prophylactically to treat IFIs in high risk patients.

The first trial reported by Professor Maertens compared posaconazole and fluconazole for prophylaxis of IFI in allogeneic HSCT recipients with GVHD who were receiving intensive immunosuppressive therapy. Patients were randomized to oral posaconazole (200 mg three times a day, 301 patients) or oral fluconazole (400 mg once daily, 299 patients). Treatment was given for 16 weeks or until a pre-specified endpoint had been reached. At the end of the 16 week period, posaconazole was found to be superior to fluconazole in preventing proven or probable invasive aspergillosis (7 cases vs. 27 cases, $p=0.006$) and as effective as fluconazole in preventing all IFIs (16 cases vs. 27 cases, $p=0.07$). Posaconazole was also superior in preventing aspergillosis (3 cases vs. 17 cases, $p=0.001$) and IFIs overall (7 cases vs. 22 cases, $p=0.004$).

The second study reported by Professor Maertens compared posaconazole with standard azoles (fluconazole and itraconazole) in neutropenic patients with newly diagnosed or first relapse of acute myelogenous leukaemia (AML) or myelodysplastic syndrome (MDS). Patients were randomized to receive oral posaconazole (200 mg, three times a day, 304 patients) or oral standard azole therapy (fluconazole 400 mg once daily {240 patients}) or itraconazole 200 mg twice daily {58 patients}) with each complete chemotherapy cycle until complete

remission or for up to 12 weeks. Commenting on the results, Professor Maertens said that the incidence of proven or probable IFIs during treatment was significantly less in the posaconazole group compared with to the standard azole group (7 cases (2%) vs. 25 cases (8%), $p=0.0009$). 'The safety profile of posaconazole was similar to the standard azoles,' he added.

Dr Oliver Cornely, University of Cologne, Germany, presented the mortality data from these two posaconazole prophylaxis studies. He said that overall mortality at 100 days in the AML/MDS study was 49 (16%) in the posaconazole arm, compared with 67 (22%) in the standard azole arms ($p=0.048$). Analysis of time to death also showed a significant survival benefit for patients receiving posaconazole ($p=0.035$). 'This is the first trial to show an overall mortality reduction in AML patients by antifungal prophylaxis. Treating these high-risk patients with posaconazole prophylactically could well reduce the incidence of invasive aspergillosis.'

Dr Cornely also reported that in the prophylaxis trial for HSCT recipients, mortality due to invasive IFIs was lower for posaconazole (1%) than fluconazole (4%) ($p=0.041$) and that both drugs were well tolerated. Dr Cornely added that this was the first randomized trial to show benefit of antifungal prophylaxis in HSCT patients with severe GVHD. When questioned about any breakthrough infections, Dr Cornely replied that data from the isolates showed that resistance was not a problem, despite long-term exposure to posaconazole.

Prophylactic, pre-emptive or empirical therapy?

One of the main challenges in treating IFIs in high-risk patients is the difficulty in obtaining a rapid and reliable diagnosis. According to Professor Georg Maschmeyer, Klinikum Ernst von Bergmann, Potsdam, Germany, there is a lack of standardised diagnostic tests with high sensitivity and specificity. 'Because of this, a diagnosis of an IFI can come too late for a successful outcome and this is why early treatment becomes so important. If you wait to treat high-risk patients

with AML/MDS and fever empirically, then the success rates are around 27%. But if you treat pre-emptively i.e. when the patient has fever + one other sign, the success rate can be as high as 78%.'

Now that there are data to show that posaconazole is effective as a prophylactic treatment for IFIs, it is possible that the ECIL guidelines will be changed.

'Posaconazole is a very good drug and may become the gold standard for treating IFIs, said Professor Maschmeyer. He added that it was a particularly valuable antifungal agent as it was effective against aspergillosis and zygomycosis. 'In the past we did not have a drug that was effective against both these infections and we had to treat one infection or the other. When voriconazole began to be used we started to see a significant increase in the incidence of zygomycosis. With posaconazole we now have a drug that can treat both aspergillosis and zygomycosis. I would certainly use it as a first line drug pre-emptively for high-risk patients.' He noted, however, that the use of fluconazole had led to fungal resistance, which was a theoretical possibility with any antifungal agent.

Posaconazole - an option for brain abscess?

Posaconazole may be a new treatment option for brain abscess, according to a poster presented at the congress by Lydia Markham et al, University Hospitals of Geneva, Switzerland. A 60-year old woman with a history of systemic sclerosis and long-term corticosteroid therapy was admitted to hospital, sleepy and confused after frequent falls. One week after admission her condition deteriorated and she showed signs of progressive right hemiparesis, aphasia and a worsening in sensorium. A cerebral biopsy was performed on day 12, which confirmed a brain abscess caused by *Cladophialophora bantiana*. High dose voriconazole (400mg every 12 hours) and liposomal amphotericin B (5mg/kg increasing to 7 mg/kg) was started. Five days after starting antifungal therapy, the lesion had increased in size, so voriconazole was replaced by posaconazole (400mg twice daily). Sixteen days after commencement of treatment the brain

lesion had reduced in size, indicating that posaconazole was effective. Unfortunately, despite an improvement in her neurological condition, the patient developed pneumonia with severe sepsis, continued to deteriorate and finally died.

Immunological approaches

Another topic discussed at the congress was immunological approaches to fungal infections. Professor Bart -Jan Kulberg, University Hospital Nijmegen, The Netherlands, said that the resolution of IFIs was often dependent on recovery from an immunological state. 'This indicates that host defence mechanisms are extremely important in the clearance of fungal pathogens. Immunotherapy, which is aimed at enhancing the host defence mechanisms, may be a way of improving the clinical outcome of invasive mycoses.' Professor Kulberg reported the results of two Phase II studies with recombinant granulocyte colony-stimulating factor (G-CSF) and interferon gamma. Recombinant G-CSF was found to reduce the infection time with candidiasis in non-neutropenic patients and interferon gamma, used as adjunctive therapy for cryptococcal meningitis, led to an improved response.

Vaccination may also be means of preventing IFIs, Professor Kulberg explained. A small study has already shown that passive vaccination together with amphotericin B produced a better response than with the antifungal drug alone, although there more toxicity was seen in the vaccination arm of the study. Active vaccination is still at an early stage of development, but Professor Kulberg speculated that it could be used in patients before they underwent a bone marrow transplant, during abdominal surgery or given to those who go in to ICU.

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