

Report from the 35th Annual Meeting of the European Group for Blood and Marrow Transplantation, Göteborg, Sweden, 29 March – 1 April 2009

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Invasive fungal infections (IFI), and particularly aspergillosis, continue to jeopardise the outcome of haematopoietic stem cell transplantation (HSCT). In Europe, the incidence of invasive aspergillosis in allogeneic HSCT recipients is nearly 3%, with a mortality of over 70%. Strategies to avert these complications were therefore a major topic at the meeting, attended by almost 4,000 delegates.

Advances in diagnosis of invasive fungal infections

Advances in diagnosis owe much to the development of non-culture-based microbiological tools. However, although these methods are quicker and more reliable than those based on culture, they have important limitations. The sensitivity of the galactomannan (GM) assay for detecting *Aspergillus* is significantly lower for *A. fumigatus* than non-*fumigatus* species. Moreover, both sensitivity and specificity depend on the index cut-off used for a positive result. This assay has a high positive predictive value (PPV) of more than 75% for detecting GM in bronchoalveolar lavage (BAL) fluid from patients with radiographic abnormalities, one of its most exacting applications. However, results are less reliable in patients receiving antifungal agents or beta-lactam antibiotics, explained Dr Kieren Marr, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Polymerase chain reaction (PCR) assays have shown high sensitivity and specificity to detect IFI but need further development and standardisation. The difficulties of diagnosing invasive aspergillosis have prompted the creation of the European *Aspergillus* PCR Initiative (EAPCRI) which is testing 12 different PCR methodologies. The participating laboratories achieved sensitivities and specificities of up to 94% and 97%, respectively, but only if they complied exactly with the protocol, reported Dr Peter Donnelly, Nijmegen University Centre for Infectious Diseases, Nijmegen, The Netherlands. PCR amplification methods perform consistently and almost all PCR methods are able to detect low DNA, he said.

But Dr Marr warned that when the population IFI prevalence is only 10%, even the most sensitive and specific test cannot achieve a positive predictive value > 40%. However, even if the prevalence is low, the negative predictive value of such a test remains high. So, rather than using a positive test to guide antifungal therapy, “I think we need to ...ask a different question: when is it safe to withhold antifungal therapy with a negative test?”

Primary antifungal prophylaxis

Given these diagnostic problems, there is growing interest in antifungal prophylaxis in high-risk patients. These include allogeneic HSCT recipients with graft-versus-host disease (GvHD) and relapsed leukaemia patients. Various guidelines give an A1 recommendation for both fluconazole and posaconazole in these settings.

Posaconazole has anti-mould activity and a better drug-drug interaction profile than fluconazole explained Dr Johan Maertens, Gasthuisberg University Hospital, Leuven, Belgium.

Prevention rather than treatment of any fungal disease is justified, Dr Maertens continued, when the incidence of disease is high – and therefore the number needed to treat (NNT) is low – when the consequences of the disease are serious, when diagnosis is difficult and when the cost of treatment is greater than the cost of prophylaxis.

Itraconazole

Pre-engraftment, there is no recommendation for posaconazole prophylaxis, which may warrant the use of other strategies. One recent study used itraconazole backed by high-resolution computerised tomography (HRCT) in patients developing neutropenic fever >72 hours. If the HRCT was positive or there was clinical suspicion of IFI, then the patients received caspofungin, followed by a repeat CT 10 – 14 days later and then, depending on the findings, either step-down therapy to voriconazole or a switch to liposomal amphotericin B. Of the 99 HSCT patients in the study, 53 (54%) had prolonged neutropenic fever. However, and based on positive HRCT findings, only 17 (17%) received broad-spectrum antifungal therapy with caspofungin. This represented a 68% reduction in antifungal use at the cost of a single IFI death (in the caspofungin group).

Posaconazole

Post-engraftment HSCT recipients – and particularly those receiving potent immunosuppression for GvHD – are at high risk of developing mixed infections, which are difficult to diagnose. “This population clearly needs some kind of prophylaxis,” Dr Maertens said. “And following the recommendations, that would be posaconazole prophylaxis.” He warned, however, that antifungal prophylaxis could interfere with diagnostic tests and that therefore physicians must choose between a diagnostic and a prophylactic approach.

Professor Oliver Cornely, University Clinic, Cologne, Germany, agreed with stratifying patients according to risk. The ones at highest risk are those with acute myeloid leukaemia (AML) undergoing induction chemotherapy. Professor Cornely was lead investigator of the pivotal study on posaconazole prophylaxis in such patients [1]. “During the consolidation period, the risk is low and we can go for the diagnostic approach. If GvHD occurs, then we switch over to posaconazole.” He also agreed about the need to choose between diagnosis and prophylaxis; the GM assay will always be negative in patients receiving posaconazole, he said.

The efficacy and safety of posaconazole prophylaxis post-engraftment received further endorsement from a group from Salamanca, Spain, who reported on 37 allogeneic HSCT patients, of whom 65% had GvHD. No patient developed a proven IFI and probable IFI was reported in only one.

Another Spanish group has extended the potential indications for primary posaconazole prophylaxis to the early high-risk period after allogeneic HSCT. Posaconazole prophylaxis is highly cost-effective in this setting, report Dr Rafael Duarte, Hospital Duran i Reynals, Barcelona, and colleagues. In their study of 43 consecutive allogeneic HSCT recipients, prophylaxis failure was common in the patients receiving itraconazole, with 12.5% developing a proven/probable IFI compared with none of the posaconazole group. The probability of early IFI-free survival at day 100 was superior (85% vs. 56%; $p=0.012$) and the probability of overall survival at day 100 showed a statistical trend towards an improved outcome

in the posaconazole group (85% vs. 63%; $p=0.09$). The group calculated an incremental cost-effectiveness ratio (ICER) of posaconazole vs. itraconazole per IFI avoided of €5,111 per IFI-free patient and €7,411 per surviving patient. The ICER represents the additional cost of one unit of outcome gained – such as a quality of life-adjusted year – by a health care intervention when compared with the next best alternative.

Voriconazole

An as-yet unpublished prophylaxis study has failed to demonstrate superiority for voriconazole vs. fluconazole. Dr Marr, who alluded briefly to the findings during a Q&A session, noted that the study, in 600 patients, showed the “same kinds of trends” to a decrease in IFI as observed in the large posaconazole prophylaxis studies. The endpoint, however, was a composite – fungal-free survival – and differed from that used in all previous prophylactic studies. “It will be a matter of controversy as to whether you see this as a failed study or a successful study using a different type of trial design” she said.

In addition, anxiety continues about the emergence of resistant and/or unusual fungal species under voriconazole prophylaxis. A study of HSCT recipients at the Ramban Health Care Campus, Haifa, Israel, revealed a zygomycoses prevalence of 4%. Of the six patients affected, five had received voriconazole. “In addition to the known predisposing factors for *Mucor* infection, previous use of voriconazole may increase the incidence and should raise suspicion,” say the researchers.

Secondary prophylaxis

Secondary prophylaxis has a role in patients at risk of recurrent IFI. In a recent study, voriconazole was given to 45 adult allogeneic HSCT patients with previous or probable IFI within the previous 12 months and treated in 17 centres in 8 European countries. Three cases of IFI were recorded after transplant: one each of *Candida albicans* and *Scedosporium prolificans* (the latter patient died), both of which were recurrent infections, and a *Mucor* spp zygomycosis, which was a new infection. This represents a crude IFI incidence of only 7%, which compares favourably with the 30% expected after transplant, reported Professor Catherine Cordonnier, Hôpital Henri Mondor, Créteil, France.

Dr Jacqueline Cornish, Bristol Royal Hospital for Children, UK, described a novel approach to secondary prophylaxis in children. She explained that in children, as in adults, the increasing intensity of therapy leads to a higher incidence of IFI with *A. fumigatus*. Diagnosis is particularly problematic in children, due to variable GM antigenaemia and PCR findings and the frequent absence of cavitation, air crescent or halo signs on CT. A history of invasive aspergillosis has become a contraindication to BMT in some centres because of these difficulties and the high risk of recurrence. However, since Dr Cornish introduced secondary prophylaxis with granulocytes and liposomal amphotericin B into her practice in 1997, there have been no IFI deaths and 15 (48%) of the 31 children treated this way are still alive.

Dr Cornish does not use posaconazole for prophylaxis, due to the lack of paediatric data. “We would very much like to use it. In the future I would like to see a trial which included children. I think it is one of the most interesting agents around and I think it will in the future have a very key role in prophylaxis.”

Therapeutic drug monitoring for azoles

Therapeutic drug monitoring (TDM) remains controversial. Professor Cornely explained that, in healthy volunteers, steady-state levels of posaconazole were approximately 33 times higher in alveolar cells than in the plasma and up to 2860 times higher than the MIC₉₀ for *Aspergillus* spp [2]. Results from his own institution show no correlation between breakthrough infections and posaconazole serum levels. There is therefore no rationale for posaconazole TDM, Professor Cornely suggested.

The argument against TDM applies equally to the other azoles as Dr Peter Donnelly made clear at another session. There is no evidence that the results will alter clinical decision making, he said. “I would have to conclude that you shouldn’t actually be doing therapeutic drug monitoring at the moment.”

Revised invasive fungal infection definitions

Recent revisions to the definitions of IFI could have major implications for researchers and clinicians. The revisions, from the European Organisation for

Research and Treatment of Cancer (EORTC)/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG), include additions of host, clinical and mycological factors to the 'probable' category, and a stricter definition of the 'possible' category. The list of host factors now omits fever-based criteria. More than four days of unexplained fever despite broad-spectrum antibiotics "doesn't mean you have fungal infection or fungal disease," said Dr Maertens who is past chair of the EORTC Infectious Diseases Group. New mycological criteria encompass beta-D-glucan in blood as well as in bronchoalveolar lavage (BAL) fluid and cerebrospinal fluid (CSF).

Application of the revised criteria to 330 patient-episodes at St Bartholmew's Hospital, London, yielded somewhat surprising findings, reported Dr Dimitris Tsitsikas, from Barts and the London NHS Trust. Overall, the number of positive episodes (possible, probable and proven) were 65% less with the new than the old criteria, with a 69% drop in 'possible' IFI and a 70% fall in 'probable' diagnoses. "A group of patients may be over- or under- treated, depending on which set of definitions you use," Dr Tsitsikas said.

References

1. 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
2. Conte JR Jr, Golden JA, Krishna G, McIver M, Little E, Zurlinden E. Intrapulmonary pharmacokinetics and pharmacodynamics of posaconazole at steady state in healthy subjects. *Antimicrob Agents Chemother* 2009;53:703–7