

Report from 34th Annual Meeting of the European Group for Blood and Marrow Transplantation, Florence, Italy, 30 March - 2 April 2008

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Haematopoietic stem cell transplantation (HSCT) is widely used in the treatment of blood and lymphoid cancers, and a range of other immune diseases, with more than 30,000 autologous and 15,000 allogeneic procedures performed annually worldwide. But, as some 5000 delegates at the recent 34th Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT) congress heard, success is hindered not only by a shortage of fully matched grafts, but by complications such as invasive fungal infection (IFI) associated with the prolonged immunosuppression that accompanies HSCT.

High-risk groups for aspergillus infection

IFI is six times more common in patients undergoing HSCT than those who have autologous grafts, and the risk is also raised in patients who have umbilical cord blood transplants, according to data presented at the congress.

Professor Livio Pagano, from the Policlinico Gernelli, Rome, Italy, reported an IFI rate of 3.8% in a retrospective cohort study of transplant patients treated at 11 Italian centres – 7.8% in those undergoing allogeneic transplants, compared to 1.2% in those who had an autologous graft. Aspergillosis mortality was also higher in allogeneic than autologous transplant patients – 77% and 14% respectively – with candidaemia associated with fewer deaths and less variation between the two types of transplant (57% and 44% respectively).

Data from a retrospective analysis of 306 patients undergoing HSCT from unrelated donors (60%), family mismatched (23%), mismatched unrelated (11%) or cord blood (6%), presented by Dr Anna Maria Raiola from St Martino's Hospital, Genoa, Italy, confirmed the excess risk of invasive aspergillosis (IA) in allogeneic transplants. In the study, 37 patients had probable and 8 had proven IA, with a prevalence of 15%. The median time to onset was 53 days after HSCT

(range 4-449 days), with infections roughly divided between early and late onset. Mortality was 76%, with 67% related to IA, and IA the primary cause in 40%. Late take of neutrophils and steroid therapies were related to increased risk of IA, and ATG use in the conditioning regimen, steroid therapy, relapse, IgA and cholinesterase at diagnosis of IA were all identified as predictors of survival.

Dr Raiola concluded that that IA is associated with high mortality, especially in patients whose immune system does not recover after HSCT.

Empirical versus pre-emptive antifungal therapy?

Pre-emptive antifungal therapy is a cost-effective alternative to empirical therapy in patients who are neutropenic for relatively short periods (under 15 days), but further refinement of diagnostic techniques is needed before it can be recommended more widely for patients who are likely to have a low neutrophil count for more prolonged periods.

This was the conclusion of Professor Catherine Cordonnier, from the Hôpital Henri Mondor, Paris, France, at the end of a presentation during which 38% of the audience said that they used pre-emptive treatment in allogeneic HSCT patients and 34% said they used the empirical approach.

Professor Cordonnier's advice was based on the results of the PREVERT study, which compared empirical and pre-emptive treatment in 293 patients with haematological malignancies and an expected period of neutropenia of 10+ days during their treatment. All were screened twice weekly for galactomannan antigen.

Seventeen patients in the study had an IFI, 4 (2%) in the empirical group and 13 (9%) in those receiving pre-emptive therapy ($p < 0.02$), though the overall survival rate was comparable ($p = 0.12$). Further investigation revealed that there was no difference in infection rate between the two treatment approaches when

neutropenia was short. But the longer the period of neutropenia, the greater was the risk of infection with pre-emptive therapy.

Professor Cordonnier therefore recommended that future pre-emptive strategies should include more refined techniques – imaging tools or biological markers – to increase diagnostic accuracy. She added that pre-emptive treatment should be evaluated against prophylactic approaches.

Guidelines updates

At an EBMT Infectious Diseases Working Party session held at the congress, Professor Cordonnier introduced the recently updated European Conference on Infection in Leukaemia (ECIL-2) guidelines, which elaborated on the original guidance on the prophylaxis and treatment of infection complications in leukaemia patients produced in 2005.

At a consensus meeting of 52 experts from 24 European countries and Australia, held in 2007, level A1 evidence-based recommendations for antifungal prophylaxis in allogeneic HSCT or induction chemotherapy of acute leukemia were made for posaconazole 200 mg tid oral or fluconazole 400 mg qd iv/oral.

Equivalent (A1) recommendations for empirical treatment of fungal infection were made for liposomal amphotericin B 3mg/kg or caspofungin 50mg. For first line treatment of invasive pulmonary aspergillosis, ECIL-2 made an A1 recommendation for voriconazole 2 x 6 mg/kg D1 then 2 x 4 mg/kg. No specific treatment received an A1 recommendation for salvage therapy, but posaconazole, caspofungin and voriconazole all received BII recommendations.

The ECIL-2 recommendations are broadly similar to those of the Infectious Diseases Society of America (IDSA), published earlier this year, and discussed at the EBMT congress.

Cost effectiveness of antifungal prophylaxis

Putting key European and US recommendations for antifungal prophylaxis into practice falls well within internationally accepted cost-effectiveness thresholds, according to new data, presented by Professor Helmut Ostermann from the University of Munich Hospital, Germany.

He calculated that, in Germany, it costs €21,073 to treat an invasive fungal infection, in terms of hospital stay, diagnostic tests, blood products, antifungal and other therapies. Against this background, he analysed the cost per quality adjusted life year (QALY) of using posaconazole for antifungal prophylaxis, in line with the ECIL2 and IDSA guidelines.

Taking account of all treatment costs and the impact of induction chemotherapy and HSCT on quality of life, Professor Ostermann showed that the cost per QALY of using posaconazole instead of the previous standard treatment, itraconazole, was €8,342. This compares with the €30,000-€50,000 per QALY threshold generally accepted by government health services for new therapies.

Professor Ostermann added that similar analyses have been carried out in a number of other countries, with cost savings calculated for using posaconazole instead of itraconazole in the USA, Canada, Spain, Scotland, the Netherlands, Switzerland and France, and a cost per QALY of €1,173 in Belgium.

The Swiss experience

Using clinical trial data for a cost-effectiveness analysis of posaconazole versus standard azole therapy for the prevention of IFI in high-risk patients in Switzerland, health economist Dr Roger-Axel Greiner and colleagues reported a mean cost saving of CHF 1,118 in neutropenic patients (CHF 9,089 vs 10,207) switched to posaconazole. In haematological patients with GVHD, switching to posaconazole was associated with a CHF 7041 increase in costs (CHF 17,720

vs 10,679). But, at CHF 48,324, the cost per life year saved fell below the CHF 60,000 threshold accepted as cost effective.

The Spanish experience

In another demonstration of the impact of guidelines implementation, Dr Rafael Duarte, from the Hospital Duran i Reynals, Barcelona, Spain, reported that switching from itraconazole to posaconazole prophylaxis in allogeneic HSCT patients reduced prophylaxis failure and improved fungal infection survival, with a trend towards an improvement in overall survival. None of 13 consecutive patients given posaconazole prophylaxis since guidelines implementation in June 2007 required additional antifungal treatment for infection within 100 days of their transplant, compared with 31% of 13 consecutive patients who received itraconazole prophylaxis before guidelines implementation ($p=0.04$). Fungal infection-free survival was 85% at 100 days in the posaconazole group, compared to 46% with itraconazole ($p=0.03$). Overall survival was 85% and 69% respectively ($p=0.08$).

Dr Duarte concluded that posaconazole was well tolerated with no significant toxicity, though he drew attention to the need to reduce the dose of cyclosporin A in patients using this anti-rejection drug, because of its interaction with posaconazole.

Future directions

- A key study aimed at determining which part of the DNA extraction process needs to be improved in order to make *Aspergillus* PCR testing more practicable is expected to get underway in the next few months. Outlining the study, Professor Peter Donnelly, from Radboud University Nijmegen Medical Centre in The Netherlands, updated delegates on the progress of the *Aspergillus* PCR Working Group of the International Society for Human and Animal Mycology (ISHAM). He explained that an initial review had concluded that DNA extraction rather than the

performance of the various PCR techniques is the main obstacle to wider use. The extraction process will therefore be explored at 24 centres, and the basic requirements for clinical validation have also been agreed. Professor Donnelly reported that it is hoped to propose a new standard for PCR testing by early 2009.

- Serial galactomannan results could prove a useful predictor of survival in patients with IFI, and tests should be included in future treatment studies, concluded Dr Johan Maertens, from the University Hospital Gasthuisberg, Leuven, Belgium. He presented data from two recent studies showing that galactomannan index (GMI) correlates well with survival. In the first study, in 56 adults with haematologic cancer receiving antineoplastic therapy, there was a strong correlation between survival outcome and GMI ($p < 0.0001$), and the results were comparable for neutropenic and non-neutropenic patients. A similar finding has been reported in a second study of 43 patients. But data from larger numbers of patients are now needed, said Dr Maertens.

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