

## Antifungal Treatment in the Blood and Marrow Transplant Setting – Perspectives from Clinical Experience

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Invasive fungal disease (IFD) is a major threat to the success of haematopoietic stem cell transplantation (HSCT), especially in the modern era of reduced-intensity conditioning regimens and wide range of donor sources. Changing fungal epidemiology and mortality rates of 80–90% for certain pathogens<sup>1</sup> are adding to the challenge for haematologists and oncologists. Against this background, speakers at the symposium 'Antifungal treatment in the bone marrow transplant (BMT) setting: Perspectives from clinical experience', held during the 36th Annual Meeting of the European Group for Blood and Marrow Transplantation in Vienna, Austria on 21–24 March 2010, presented data showing the impact of recent epidemiological and clinical IFD studies on everyday practice in Europe and the US.

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### Who Is At Risk and Why?

Daniel Couriel (The Sarah Cannon Cancer Center, Nashville, TN, US) reviewed recently published data from the Transplant Associated Infection Surveillance Network (TransNet) of 23 US transplant centres, which showed a 12-month cumulative incidence of invasive fungal infection (IFI) among 15,820 HSCT patients of 3.4%.<sup>2</sup> Although this is relatively low, Couriel pointed out that the infection rate in subsets such as allogeneic transplant patients was over six times higher than in those undergoing autologous transplants (8.1% for mismatched related allogeneic versus 1.2% for autologous HSCT).

TransNet data show that invasive aspergillosis (IA) is the biggest threat to HSCT patients. A total of 983 IFIs were identified among 875 HSCT recipients, 43% of which were IA, 28% invasive candidiasis and 8% zygomycosis; other moulds were responsible for 7% of infections and unspecified moulds for a further 6%.<sup>2</sup>

Couriel explained that further analysis demonstrated the prolonged period during which patients were at risk of some types of IFD. He highlighted the importance of continued awareness and observation, pointing out that, while candidaemia was diagnosed a median 61 days after transplantation, IA was diagnosed a median 99 days, fusarium 123 days and zygomycosis 135 days after transplantation.<sup>2</sup>

Couriel pointed out that most risk factors for IFD in HSCT patients are host-related, notably neutropenia related to immunosuppression caused by chemotherapy or prolonged steroid treatment and acute or chronic graft-versus-host disease (GVHD) arising from disruption of immune reconstitution.

### Changing Definitions

Andrew J Ullmann (Johannes Gutenberg University, Mainz, Germany) reviewed the revised European Organisation for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) definitions for 'proven', 'probable' and 'possible' IFD published in 2008, which

have expanded the definition of probable disease and reduced the scope of the possible category.<sup>3</sup> Probable IFD requires the presence of a host factor (e.g. recent neutropenia or receipt of allogeneic HSCT), a clinical criterion (e.g. computed tomography [CT] signs of lower respiratory tract fungal infection, evidence of sinonasal or central nervous system [CNS] lesions or disseminated candidiasis) and a mycological criterion (e.g. positive culture or cytology or antigen detection). By contrast, a possible IFD requires only the presence of appropriate host factors and sufficient clinical evidence consistent with IFD (i.e. the presence of pulmonary infiltrates only is insufficient; fungal 'typical' infiltrates would be required) but for which there is no mycological support. Proven IFD requires demonstration of fungal elements in diseased tissue, which can include results of indirect assays that are highly specific for the infection being detected.

As Ullmann explained, revised definitions of IFD, variations in the way that treatment success is defined and the adverse effects of host factors, such as low Karnofsky score and the absence of halo sign, all need to be considered when deciding how best to apply clinical trial evidence to everyday practice.

### Antifungal Treatment Strategies for Haematopoietic Stem Cell Transplantation Patients

With aspergillosis the most likely fungal challenge for clinicians managing HSCT patients, members of the symposium faculty assessed the effectiveness of the current options for first-line treatment recommended by US and European guidelines – voriconazole or liposomal amphotericin B (L-Amb).<sup>4,5</sup>

Ullmann compared response and survival data from two key studies of voriconazole and amphotericin B.<sup>6,7</sup> In a randomised, unblinded comparison of intravenous (IV) voriconazole and IV amphotericin B deoxycholate, complete or partial responses at 12 weeks were 53% for voriconazole-treated patients and 32% for amphotericin B-treated

patients, with survival of 71 and 58%, respectively.<sup>6</sup> In a subsequent double-blind comparison, complete or partial responses were seen in 50% of patients taking L-Amb 3mg/kg, with a survival rate at 12 weeks of 72%.<sup>7</sup> Additional analysis of this study revealed that survival was significantly worse in patients undergoing allogeneic HSCT than in those receiving autologous transplants (40% versus 71%;  $p < 0.001$ ).

Ullmann pointed out that comparable response and survival rates were achieved in two recently published studies of caspofungin for the treatment of IA in haematological malignancies and allogeneic HSCT patients.<sup>8,9</sup> In an EORTC phase II study of adults with haematological malignancies and proven or probable IA, complete or partial responses at the end of treatment were seen in 33%, stabilisation of IFD in 15% and progression in 51%.<sup>8</sup> The six- and 12-week survival rates were 66 and 53%, respectively.

In the second study in allogeneic HSCT patients, 42% of patients had complete or partial responses at the end of caspofungin therapy (median 24 days), and 4 and 50% had stable and progressing disease, respectively.<sup>9</sup> At week 12, 33% of patients had complete or partial responses, and survival rates at weeks six and 12 were 79 and 50%, respectively.

## The Need for Prophylaxis

Given that successful outcomes are achieved with first-line IA therapy in only about half of HSCT patients, antifungal prophylaxis has been widely introduced at transplant centres in Europe and the US, and symposium speakers discussed the results of the pivotal studies that underpin current European and US prophylaxis recommendations.<sup>4,10</sup>

Rafael de la Cámara (Hospital de la Princesa, Madrid, Spain) presented data from a systematic review and meta-analysis of 64 good-quality randomised controlled trials (RCTs) in nearly 13,000 cancer patients undergoing chemotherapy or HSCT.<sup>11</sup> This showed that antifungal prophylaxis significantly decreased all-cause mortality compared with placebo, no treatment or non-systemic antifungal agents, with a relative risk (RR) of 0.84 (95% confidence interval [CI] 0.74–0.95). In allogeneic HSCT recipients, prophylaxis reduced all-cause mortality (RR 0.62, 95% CI 0.45–0.85), fungal-related mortality and documented IFD.

Further analysis showed the benefits of antifungal agents with antimould activity. Compared with antimould drugs, fluconazole was associated with a higher risk of IFI (RR 1.53), documented *Aspergillus* (RR 2.1) and IFI-related mortality (RR 1.53), together with a trend towards greater overall mortality (RR 1.14).

Ullmann and Couriel discussed studies that compared the effects of antifungal prophylaxis with fluconazole, posaconazole, itraconazole and voriconazole in HSCT patients.<sup>12–14</sup>

In a large RCT of 600 patients with GVHD who were receiving immunosuppressive therapy, posaconazole was shown to be more effective than fluconazole in preventing IA and reducing IFD mortality.<sup>12</sup> At the end of the fixed 112-day treatment period, the incidence of all IFIs was 5.3% with posaconazole versus 9% with fluconazole ( $p = 0.07$ ), while the incidence of proven or probable IA was 2.3 and 7%, respectively ( $p = 0.006$ ). During the time that patients were receiving study medications, fewer breakthrough IFIs were seen with posaconazole than with fluconazole (2.4% versus 7.6%;  $p = 0.004$ ),

particularly IA (1.0% versus 5.9%;  $p = 0.001$ ). Overall mortality was similar in the two groups, but IFI-related mortality was lower with posaconazole (1% versus 4%;  $p = 0.046$ ).

In an RCT of 600 allogeneic blood and marrow transplant patients, the cumulative rates of proven, probable and presumptive IFI were similar for voriconazole and fluconazole at six months (6.6 and 10.6%, respectively;  $p = 0.11$ ).<sup>13</sup> At 12 months, IFI rates were also similar (11.6 and 13.1%, respectively;  $p = 0.50$ ). No significant difference was seen in fungal-free survival rates between the two treatment groups at six months (78 and 76%, respectively) or at 12 months (63 and 65%, respectively).

Ullmann pointed out that data from both these clinical trials have only been presented at meetings to date and that their full publication is awaited.

In a prospective, open-label study of itraconazole and voriconazole in 489 allogeneic HSCT patients, the primary end-point was the success of prophylaxis at day 180 (defined as survival without proven/probable IFI or discontinuing prophylaxis for >14 days during the first 100 days).<sup>14</sup> Among the voriconazole-treated patients, 49.1% achieved this end-point compared with 34.5% of those using itraconazole ( $p = 0.0004$ ). There was no significant difference in survival between the two groups at day 100 (94% in both groups) or at day 180 (85% in both groups).

## Additional Considerations for Prophylaxis

Charles Craddock (Queen Elizabeth Hospital, Birmingham, UK) welcomed the growing range of antifungal options for HSCT patients, but urged that greater attention be paid to the pharmacokinetics of different agents and their potential to interact with other drugs that HSCT recipients are likely to be taking. He added that prophylactic regimens will need to be tailored to different high-risk populations and should not be seen in isolation from other downstream treatments.

He presented data showing that increased exposure to cyclosporin during the early post-HSCT phase is associated with increased relapse risk ( $p < 0.0001$ ) and decreased overall survival ( $p < 0.0001$ ).<sup>15</sup> Within this context, Craddock discussed the results of a recent study of concentration/dose ratios for cyclosporin and tacrolimus in allogeneic HSCT patients treated with voriconazole, which showed changes ranging from -9.4 to 266.9% for cyclosporin and from 25.4 to 307.6% for tacrolimus.<sup>16</sup> He stressed the importance of monitoring levels of cyclosporin or other calcineurin inhibitors to ensure that they are not adversely affected by antifungal treatment.

Turning to the growing need for secondary antifungal prophylaxis, Craddock pointed out that fungal reactivation makes a major contribution to transplant-related mortality in patients with a history of possible/proven IFD. He explained that prolonged duration of neutropenia, advanced-stage disease and short time between previous antifungal treatment and transplantation are the strongest predictors of secondary fungal infection. Patients undergoing bone marrow or cord transplantation appear to be at higher risk than those undergoing peripheral stem cell transplantation; those with GVHD also seem to be at greater risk.

Craddock also discussed the results of the voriconazole for secondary prophylaxis of invasive fungal infection (VOSIFI) study, an

open-label study of 45 adult allogeneic HSCT patients with previous proven or probable IFI within the 12 months prior to transplantation.<sup>17</sup> Median duration of voriconazole treatment was 94 days, and a secondary infection rate of 7% was recorded.

### Prophylaxis – The German Experience

Ullmann presented data from his own practice on 52 allogeneic HSCT patients who received posaconazole prophylaxis for the first 100 days after transplantation during 2008. Of this group, almost two-thirds had no evidence of fungal infiltrates, while one-quarter had possible IFD and fewer than one-tenth had probable IFD. Among patients whose blood levels of posaconazole were measured, the mean level was higher in patients without infiltrates. Mortality was higher in those with proven/probable infection (more than half of the patients) than in those without infiltrates.

Ullmann concluded that good compliance apparently correlated with lower levels of IFD, and suggested that, despite the preliminary nature of the data, higher levels of drug exposure may give better protection. He added that there appeared to be a link between a lack of infiltrates and better survival.

### Prophylaxis – The Spanish Experience

de la Cámara discussed the results of a recent survey in 55 HSCT centres in Spain, which showed that clinicians are well aware of European and US recommendations for IFD prevention but are offering antifungal prophylaxis to a wider range of HSCT patients than those highlighted in the guidance. Thirty-eight per cent of responders felt that universal IFD prophylaxis was justified when there was an IFI incidence of 6–10%, and 44% felt that universal prophylaxis was justified when the IFI incidence was 11–15%.

Fluconazole was the drug of choice for prophylaxis in autologous HSCT patients, while there was a shift towards use of mould-active agents in allogeneic HSCT patients. For acute myeloid leukaemia patients undergoing allogeneic HSCT, 40% of respondents used posaconazole, 27% itraconazole prophylaxis and 19% fluconazole. For patients undergoing allogeneic HSCT with  $\geq$ grade II GvHD, 80% used posaconazole and 11% voriconazole. There was strong support within Spanish HSCT centres for monitoring plasma levels of azoles, with 69% supporting measurements for selected cases and 15% considering that it should be performed for all patients.

de la Cámara also presented the results of a study of antifungal prophylaxis use in 198 HSCT patients undergoing treatment at the same 55 Spanish centres, which showed the reality of clinical practice. Ninety-three per cent of allogeneic and 78% of autologous HSCT patients had antifungal prophylaxis and, despite the strong support for mould-active drugs in allogeneic patients in the original survey, 46% of this group were receiving fluconazole and 54% antimould agents.

Results of a further study of 135 allogeneic HSCT patients treated at 10 Spanish hospitals with posaconazole prophylaxis confirmed in 'real life' the findings from previous studies – notably that IFI and survival rates were comparable to those seen in posaconazole randomised prophylaxis trials. Proven/probable IFI was demonstrated in 3.5% of 112 patients treated with posaconazole as primary or secondary prophylaxis and possible IFI in 7%. IFI-related mortality in the total group of 135 patients was 3% and overall mortality was 30%.

## The Role of Empirical and Pre-emptive Therapies for Neutropenic Patients

Despite the reductions in IFD and IFD-related mortality that have been achieved with antifungal prophylaxis, improved strategies are still needed for the prompt treatment of possible IFD in neutropenic patients with persistent fever despite broad-spectrum antibiotics.

Craddock reviewed the widespread use of empirical antifungal therapy for such patients and highlighted the lack of consensus on the optimal approach. Current European guidelines support the use of a wide range of antifungal agents for empirical therapy, with the strongest evidence in support of caspofungin and liposomal amphotericin B.<sup>18</sup>

Craddock drew attention to the growing interest in pre-emptive therapy based on the results of non-culture-based tests, such as galactomannan (GM), (1-3)- $\beta$ -D-glucan, polymerase chain reaction (PCR) and high-resolution CT (HRCT).

He reviewed a series of recent studies suggesting that the pre-emptive approach may reduce the number of patients who are treated with antifungal therapy in response to persistent fever. In a study of pre-emptive therapy in high-risk neutropenic patients based on GM, HRCT and bronchoscopy with lavage (BAL), antifungal therapy was reduced by 78%.<sup>19</sup> In a second study, high-risk, febrile neutropenic patients who had pre-emptive treatment for IFD based on clinical, imaging or GM evidence had more IFD (9.1 versus 2.7%) but similar survival rates (95.1 versus 97.3%) compared with those who received empirical therapy.<sup>20</sup>

However, as Craddock pointed out, considerable variability has been reported in the results of non-culture-based diagnostic tests, and it can be difficult to determine the applicability of the results of pre-emptive studies to clinical practice at other centres. In addition, it can be difficult for clinicians to obtain funding for new diagnostic services such as GM or PCR testing.

### The UK Experience

Craddock showed that in the UK, where GM testing is not widely available, pre-emptive treatment guided by the results of HRCT has been shown to reduce the need for antifungal drugs without jeopardising survival.<sup>21</sup>

He reported the results of pre-emptive treatment in 99 consecutive patients in whom HRCT was used as the diagnostic test to predict need for treatment. All patients received itraconazole prophylaxis (or voriconazole if they had a previous infection), and those who developed neutropenic fever  $>$ 72 hours afterwards or in whom there was suspicion of IFI received HRCT. Those with negative HRCT received no additional antifungal treatment, while patients with a positive HRCT were switched from their azole to caspofungin. HRCT was repeated after 10–14 days and, if worse, patients were transferred to liposomal amphotericin B. Patients whose HRCT improved were switched to voriconazole.

Seventeen of the 99 patients (17%) received pre-emptive antifungal treatment based on their HRCT results. This compared with 53 of 99 (54%) who would have received empirical treatment based on their neutropenic fever and suspicion of IFD. Craddock reported that the HRCT-guided pre-emptive approach therefore resulted in a 68% reduction in antifungal usage in the early post-transplant period.

Eleven of the 17 patients who received caspofungin responded to treatment, and 10 of these were alive at 100 days. Of the six patients who required second-line treatment, four patients responded and four were alive at 100 days.

Craddock stressed the need for a reliable HRCT service for the pre-emptive approach to be successful, with scans performed very early and same-day reporting available.

## Conclusions

The faculty concluded that important advances are being made in the understanding, prevention and management of IFD in HSCT patients. However, progress is still needed to establish how best to apply evidence from clinical trials into routine practice, given the

variations in clinical, therapeutic, environmental and financial factors that apply at different centres. It is clear that once IFD is established the results of treatment are far from optimal, but that antifungal prophylaxis, especially with mould-active agents, can reduce IFD and, with some drugs, affect mortality.

Future developments in non-culture-based diagnostic methods will inform the relative roles of prophylactic, pre-emptive and empirical therapies, but the limited availability and uncertain reliability of some of these methods is restricting their current usage. Wider implementation of new approaches will require good communication within a multidisciplinary team, including haematologists, radiologists, pathologists and chest physicians, to ensure optimal patient care. ■

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