Secondary antifungal prophylaxis in paediatric allogeneic haematopoietic stem cell recipients

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Objectives: Presumed or proven invasive pulmonary aspergillosis (IPA) is an important cause of infectious morbidity in patients with acute leukaemia. Although prior IPA is not a contraindication for subsequent allogeneic haematopoietic stem cell transplantation (HSCT), its management during granulocytopenia and immunosuppression remains challenging.

Patients and methods: In the absence of an evidence-based approach, 11 adolescents (11–18 years) with acute leukaemia and a history of antecedent possible (4) or probable (7) IPA received liposomal amphotericin B (LAMB; 1 mg/kg once a day) from the start of the conditioning regimen until engraftment and ability to take oral medication, followed by oral voriconazole (200 mg twice a day) until the end of the at-risk period. Nine patients had a good partial response (>50% reduction in pulmonary infiltrates) and two had a complete response prior to HSCT.

Results: The median duration of intravenous treatment with LAMB was 30 days (range, 19–36), followed by a median of 152 days (range, 19–210) of oral voriconazole. LAMB was discontinued early in one patient and voriconazole was transiently or permanently discontinued due to adverse events/new contraindications in two and two patients, respectively. At +180 days post-transplant, eight patients were alive, six with complete, and one each with near complete and ongoing resolution of pulmonary infiltrates; all but one were in continuing haematological remission. Three patients had succumbed either to recurrent leukaemia (two) or refractory graft failure (one); whereas one of these patients had maintained a complete response, two died with secondary possible (one) or probable (one) IPA. Both patients had discontinued voriconazole early and developed IPA in lung areas involved during the primary episode.

Conclusions: This prospective paediatric series supports the notion that secondary antifungal prophylaxis for possible or probable IPA can be safely achieved in allogeneic HSCT. In the absence of chronic graft-versus-host disease, breakthrough infection appeared to be associated with recurrent leukaemia/graft failure and shorter duration of post-engraftment prophylaxis.

Keywords: mycoses, stem cell transplantation, voriconazole, amphotericin B

Introduction

Invasive aspergillosis has emerged as an important cause of morbidity and mortality in paediatric patients undergoing treatment for haematological malignancies, particularly those with acute myeloblastic leukemia.1–6 Although the primary control of these infections may have improved through advances in early diagnosis and the availability of more effective antifungal agents,7 the risk of recurrent Aspergillus infections following further myelotoxic chemotherapy or haematopoietic stem cell
transplantation (HSCT) is high and associated with poor outcome. Several case series suggest that continuing antifungal therapy may reduce the risk of recurrent infection in patients with prior invasive aspergillosis and controlled disease, allowing further anticancer treatment including HSCT to proceed. However, in the absence of an evidence-based approach to secondary antifungal chemoprophylaxis, the management of these patients is not well defined and remains challenging, particularly in paediatric patients.

The advent of newer antifungal agents provides further opportunities for effective secondary prophylaxis. Although liposomal amphotericin B (LAMB) has well-established clinical safety and efficacy against invasive aspergillosis and is licensed in paediatric patients, it is available as intravenous (iv) solution only. Voriconazole is an iv and oral triazole with a broad spectrum of activity against opportunistic filamentous fungi, an acceptable safety profile, predictable drug–drug interactions, and potential usefulness for secondary prophylaxis.

Voriconazole has been licensed for use in children and adolescents in both the US and the EU, respectively, on the basis of documented safety and efficacy as salvage therapy patients refractory to, or intolerant of, conventional treatments. Voriconazole was selected for prophylaxis. Written informed consent for secondary antifungal prophylaxis using LAMB, followed by voriconazole in adolescent patients undergoing allogeneic stem cell transplantation for acute leukaemia.

Patients and methods

Study design and entry criteria

The study was a single-centre, non-comparative observational cohort analysis. Eligible patients were ≤18 years of age, were scheduled to undergo allogeneic HSCT, had a history of possible, probable or proven invasive aspergillosis acquired during antecedent chemotherapy that had responded to antifungal treatment, and were required to have no contraindications against the use of the antifungal drugs selected for prophylaxis. Written informed consent for secondary prophylaxis as a medically indicated measure of supportive care was obtained within the consent procedure for HSCT.

Antifungal treatment

Secondary prophylaxis consisted of LAMB (AmBisome™; 1 mg once a day as a 1 h iv infusion) given from the start of conditioning chemotherapy until neutrophil engraftment (absolute neutrophil count; ANC ≥ 500/μL for 3 days) and the patient’s ability to take oral medication. The dosage could be escalated to 3 mg/kg once a day if a patient developed fever persisting for ≥48 h, despite appropriate antibacterial therapy or worsening symptoms and findings suggestive of invasive fungal infection. Following completion of LAMB treatment, patients were switched to oral voriconazole (V-fend™; 200 mg twice a day with a loading dose of 400 mg twice a day on day 1), which was administered until the end of the at-risk period or occurrence of intolerance. Interruption or cessation of treatment was considered in the event of intolerance, and an alternative therapy administered as deemed appropriate by the responsible clinician. The selection of this strategy was based on the generally accepted necessity of secondary antifungal prophylaxis in patients undergoing HSCT, the documented efficacy of both agents against invasive aspergillosis, and the existence of paediatric safety data and regulatory approval.

Patient entry and monitoring

Patient entry was from July 2002 to June 2006, and follow-up was at least until day +180 post-stem cell transfusion in the case of patient survival. Data collection was accomplished with a standardized case report form. Patients were monitored with regular clinical examination, laboratory monitoring and periodic radiological assessment as provided by institutional policy. Aspergillus antigen- or PCR-based diagnostic methods were not part of this monitoring. During hospitalization, patients were housed in single, reverse isolation rooms equipped with positive air pressure and high efficiency air filters, and underwent daily clinical and biochemical assessment. Following discharge, patients were followed up at least once weekly until day +100, at least every other week between day +100 and day +180, and as dictated by clinical status thereafter. Complete clinical and laboratory workup was performed on each occasion. Fungal response was assessed both clinically and radiologically; computed tomography and plain chest radiography were performed as clinically indicated.

Assessment of antifungal efficacy

Coding of invasive fungal infections and outcome was performed by the investigators responsible for data analysis (K. A. and A. H. G.). Invasive aspergillosis was classified as possible, probable or proven according to modified EORTC/MSG criteria as used in the clinical trials of LAMB and voriconazole against invasive aspergillosis. Responses to treatment were evaluated as complete (CR), partial (PR), stable (SD) or progressive (PD) disease, as defined by RECIST criteria and as used in the clinical trials in patients with invasive aspergillosis. The primary efficacy endpoint of secondary prophylaxis was defined as the absence of recurrent or breakthrough fungal infection at day +180 post-stem cell transfusion.

Assessment of safety and tolerance

Clinical adverse events (AEs) were recorded and graded according to current Common Terminology Criteria of Adverse Events set forth by the US National Cancer Institute and rated as possibly, probably or definitely related to treatment with LAMB or voriconazole, respectively. Laboratory parameters of renal and hepatic organ function were recorded at baseline and end of treatment (EOT). In addition, the most pathological value during treatment was recorded for each parameter and patient. As adjunct to the non-parametric comparison of baseline, maximum and EOT values, increases in laboratory parameters at EOT were also graded as increased to ≥1.5 and ≥3.0 times their respective baseline value (all) and being above a pre-defined upper cut-off value (hepatic transaminases and bilirubin), respectively.

Voriconazole plasma concentrations

Steady-state trough plasma concentrations of voriconazole were assessed repeatedly at random in all patients. Voriconazole was quantified by a validated HPLC method. The lower limit of quantification (LLQ) in plasma is 0.1 mg/L. For calculation of
exposure, patient samples with detectable peaks but concentrations below LLQ were set at 0.1 mg/L.

Statistical considerations
Data were analysed by descriptive statistics if not indicated otherwise. For statistical comparisons of continuous data, the Mann–Whitney U-test was used. Comparison of categorical data was performed by Fisher’s exact test.

Results
During the 4 year enrolment period between July 2002 and June 2006, 11 of 44 patients who underwent myeloablative conditioning and allogeneic HSCT for acute leukaemia had a history of possible or probable invasive pulmonary aspergillosis (IPA; 25%). All 11 patients were enrolled in the study. There was no patient with a history of invasive aspergillosis among the remaining 31 patients undergoing allogeneic HSCT at our centre for other conditions.

Demographics and baseline characteristics
Patient demographics are summarized in Table 1. Seven of the 11 patients were female and four were male; the median age was 14 years (range, 11–18). Underlying haematological diseases consisted of acute myeloblastic leukaemia (AML) in seven (64%), and acute lymphoblastic leukaemia or acute biphenotypic leukaemia in two patients each (18% each, respectively). The majority of patients (n = 9) had achieved complete haematological remission prior to admission for HSCT.

Fungal disease characteristics
Details of the antecedent mould infection and the response status at the time of admission for HSCT are shown in Table 2. All patients had IPA, probable in seven (64%) and possible in four cases (36%), and diagnosed within a median of 11 weeks (range, 4–38) prior to the start of conditioning. Primary medical treatment consisted of standard agents, given concurrently (LAMB and caspofungin) or sequentially up to the time of admission for HSCT. None of the patients received surgery. Prior to admission for HSCT, nine patients (82%) had achieved a partial response and two (18%) a complete response to antifungal treatment.

Transplant characteristics
All patients underwent standard myeloablative conditioning regimens and received allogeneic stem cell grafts from either matched related (MRD; n = 3) or mismatched unrelated/matched unrelated donors (MMUD/MUD; n = 8) on day 0 (Table 1). Standard immunosuppressive treatment consisted of cyclosporin A given from day −1 to day +100 (MRD) or +180 (MUD and MMUD) and two (MRD) to four doses of methotrexate (MTX; 10 or 15 mg/m² once a day), administered on days +1, +3, +6 and +11. Most patients (n = 9) received granulocyte colony-stimulating factor (5 μg/kg once a day) from day +6 until neutrophil engraftment; none was
Table 2. Disease characteristics of presumed pulmonary mould infection, antifungal therapy and response status prior to admission for HSCT

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Diagnostic validity</th>
<th>Diagnostic criteria clinical</th>
<th>Diagnostic criteria microbiological</th>
<th>Occurrence</th>
<th>Weeks to HSCT</th>
<th>Medical treatment</th>
<th>Response at HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>probable</td>
<td>neutropenia, fever, multiple new bilateral nodular infiltrates, in part with halo sign</td>
<td>none</td>
<td>re-induction</td>
<td>6</td>
<td>LAMB, VCZ</td>
<td>PR</td>
</tr>
<tr>
<td>2</td>
<td>possible</td>
<td>neutropenia, fever, pleural pain, new consolidation plus several nodular infiltrates in RUL</td>
<td>none</td>
<td>re-induction</td>
<td>7</td>
<td>LAMB, VCZ</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>probable</td>
<td>neutropenia, fever, multiple new nodular infiltrates in the right lung, in part with halo sign</td>
<td>none</td>
<td>consolidation</td>
<td>4</td>
<td>CAS, VCZ</td>
<td>CR</td>
</tr>
<tr>
<td>4</td>
<td>probable</td>
<td>neutropenia, fever, multiple new nodular infiltrates in the left upper and lower lung lobe</td>
<td>hyphae on BAL</td>
<td>induction</td>
<td>31</td>
<td>DAMB, LAMB, VCZ</td>
<td>PR</td>
</tr>
<tr>
<td>5</td>
<td>possible</td>
<td>neutropenia, fever, pleural pain, multiple new bilateral focal infiltrates</td>
<td>none</td>
<td>induction</td>
<td>13</td>
<td>DAMB, VCZ</td>
<td>PR</td>
</tr>
<tr>
<td>6</td>
<td>probable</td>
<td>neutropenia, fever, new nodular infiltrates in RUL with halo sign</td>
<td>none</td>
<td>induction</td>
<td>12</td>
<td>LAMB, VCZ</td>
<td>PR</td>
</tr>
<tr>
<td>7</td>
<td>possible</td>
<td>neutropenia, fever, multiple new bilateral nodular infiltrates in both upper lobes</td>
<td>none</td>
<td>consolidation</td>
<td>6</td>
<td>LAMB, VCZ</td>
<td>PR</td>
</tr>
<tr>
<td>8</td>
<td>probable</td>
<td>neutropenia, fever, multiple new bilateral nodular infiltrates with halo/air crescent sign</td>
<td>none</td>
<td>induction</td>
<td>14</td>
<td>LAMB, CAS, VCZ</td>
<td>PR</td>
</tr>
<tr>
<td>9</td>
<td>possible</td>
<td>neutropenia, fever, multiple new bilateral nodular infiltrates</td>
<td>none</td>
<td>induction</td>
<td>11</td>
<td>LAMB, VCZ</td>
<td>PR</td>
</tr>
<tr>
<td>10</td>
<td>probable</td>
<td>neutropenia, fever, new focal infiltrates in right upper and middle lobe with halo sign</td>
<td>none</td>
<td>consolidation</td>
<td>7</td>
<td>LAMB, VCZ</td>
<td>PR</td>
</tr>
<tr>
<td>11</td>
<td>probable</td>
<td>neutropenia, fever, multiple new bilateral infiltrates, in part with halo sign</td>
<td>none</td>
<td>consolidation</td>
<td>38</td>
<td>LAMB, CAS, VCZ</td>
<td>CR</td>
</tr>
</tbody>
</table>

RUL, right upper lobe; BAL, bronchoalveolar lavage; LAMB, liposomal amphotericin B; DAMB, deoxycholate amphotericin B; CAS, caspofungin; VCZ, voriconazole; CR and PR, complete response and partial response to antifungal therapy.
supported by granulocyte transfusions. Engraftment was achieved in all patients and occurred after a median of 16 days (range, 13–22). Seven (64%) patients developed acute grade I or II graft-versus-host disease (GVHD) and received therapeutic dosages of methylprednisolone for a median of 32 days (range, 9–89). None of the patients developed chronic GVHD.

Secondary prophylaxis

The course of secondary prophylaxis in the 11 patients is summarized in Table 3. Following admission for HSCT, patients received LAMB for a median duration of 30 days (range, 19–36). Four patients were started on an initial daily dosage of 3 mg/kg based on the decision of the attending physician that this would be in the patient’s best interest. Dosage escalation due to persistent fever during granulocytopenia occurred in three of the seven patients who were started on 1 mg/kg LAMB; in addition, one patient (Patient 8) receiving initial therapy with 3 mg/kg was switched to caspofungin for persistent fever and transiently worsening pulmonary infiltrates at the time of engraftment. One patient (Patient 1) prematurely discontinued and commenced voriconazole prior to engraftment due to elevated liver enzymes and elevated serum creatinine. In none of the patients was breakthrough fungal infection observed.

Prophylaxis with voriconazole was commenced at a median of day +23 (range, +12 to +29) post-stem cell transfusion. Patients continued voriconazole for a median duration of 152 days (range 19–210) to a median of day +176 (range, +38 to +228). The most common reason for stopping voriconazole was completion of therapy (64%, n = 7), based on complete or near complete antifungal response; one patient (9%) each continued treatment until death from recurrent leukaemia (Patient 4), discontinued due to suspected hepatotoxicity (Patient 3) or discontinued due to the initiation of rifampicin (Patient 1). One patient with slowly resolving lesions (Patient 8) is still receiving voriconazole. Monitoring of voriconazole in plasma revealed considerable intra- and inter-patient variability, but measurable exposure to the drug in all patients. There was no correlation between duration of treatment and plasma concentrations (Table 3).

Patient outcome at day +180

At day +180, eight patients (73%) were alive, of whom all but one (Patient 4) were in continuing haematological remission (Table 4). Six of these patients had achieved a complete response and one patient each a near complete and ongoing partial response, respectively, to antifungal therapy. Two patients had succumbed to recurrent leukaemia, one (Patient 11; day +125) without evidence for reactivation or breakthrough infection, and one (Patient 1; day +135) with possible pulmonary IPA diagnosed 2 weeks (day +120) before death; in the latter, voriconazole had been discontinued on day +92 after a near complete response due to the start of rifampicin for disseminated tuberculosis. The remaining patient died from refractory graft failure on day +150 with sepsis syndrome, bilateral pulmonary infiltrates and abundant growth of Aspergillus fumigatus in BAL material (day +148). Antifungal prophylaxis had been discontinued after a near complete response on day +92 due to gastrointestinal problems associated with his polymorbid state. Thus, 2 of the 11 patients (18%) had a second episode of IPA, which both arose in lung areas involved during the first episode. Both patients had discontinued voriconazole early and had either leukaemia relapse or graft failure.

Patient outcome at last follow-up

At a median follow-up of +255 days post-transplantation (mean, +553; range, 125–1391), two additional patients (Patients 4 and 6) have died from recurrent leukaemia (day +201 and day +620, respectively), without breakthrough infection following complete responses to antifungal therapy (Table 4). Six patients (55%) are alive and in complete haematological remission, four with complete (n = 3) or near-complete (n = 1) resolution of pulmonary lesions and off antifungal prophylaxis, and one (Patient 8) with ongoing resolution and continuing antifungal treatment. One of the long-term survivors (Patient 3) who had a complete response to antifungal therapy had late recurrent leukaemia (day +730) and was diagnosed with proven pulmonary and cerebral A. fumigatus aspergillosis during re-induction chemotherapy at day +799 post-transplant in a lung area that had been affected during the first episode. Altogether, in this cohort of 11 patients, 3 patients eventually developed a second episode of invasive aspergillosis, accounting for an overall incidence rate of 27%. Secondary aspergillosis appeared to be associated with recurrent leukaemia/graft failure (P = 0.06, Fisher’s exact test) and a shorter duration of post-engraftment secondary prophylaxis (P = 0.01, Mann–Whitney U-test).

Safety and tolerance

During LAMB prophylaxis, discontinuation due to AEs occurred in one patient (Patient 1). The patient developed increases in serum creatinine and bilirubin to more than two and more than three times baseline values, respectively, and was switched to oral voriconazole. Similarly, prophylaxis with voriconazole was discontinued prematurely in one patient (Patient 3), who developed increases in hepatic transaminases to more than five times baseline values and who had maintained complete resolution of pulmonary findings at that time and throughout day +180 (Table 3). Two further patients had treatment interruptions due to transiently elevated hepatic transaminases (Patient 5) and transient gastrointestinal upset (Patient 8), which did not recur following re-challenge.

Clinical AEs possibly related to antifungal therapy but not leading to its discontinuation or interruption were restricted to a grade I skin rash in one patient (Patient 1) during LAMB and to grade I visual disturbances and grade I facial skin rashes in one (Patient 6) and two patients (Patients 8 and 9), respectively, during voriconazole. Increases in renal and hepatic laboratory parameters were seen in all patients during prophylaxis with LAMB and voriconazole. At the end of therapy, however, significant increases in mean parameter values were limited to serum bilirubin (P = 0.0281) during LAMB prophylaxis. Similarly, the rate of patients who had increases in renal and hepatic parameter values to three or more times baseline at the end of therapy was at an acceptable level in both treatment phases [Table S1, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)].
### Table 3. Secondary antifungal prophylaxis during admission for HSCT and post-engraftment

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Prophylaxis with LAMB during HSCT admission</th>
<th>Prophylaxis with VCZ post-engraftment</th>
<th>Mean ± SD VCZ in plasma at trough (mg/L)a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dosage (mg/kg once a day)</td>
<td>duration (days)</td>
<td>stop date (post-SCT)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>19</td>
<td>+12</td>
</tr>
<tr>
<td>2</td>
<td>1/3</td>
<td>18/10</td>
<td>+10/+21</td>
</tr>
<tr>
<td>3</td>
<td>1/3</td>
<td>20/10</td>
<td>+9/+19</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>35</td>
<td>+26</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>22</td>
<td>+15</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>36</td>
<td>+28</td>
</tr>
<tr>
<td>7</td>
<td>1/3</td>
<td>18/18</td>
<td>+11/+29</td>
</tr>
<tr>
<td>8</td>
<td>3/CAS 1</td>
<td>27/7</td>
<td>+18</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>32</td>
<td>+23</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>26</td>
<td>+26</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>33</td>
<td>+26</td>
</tr>
</tbody>
</table>

LAMB, liposomal amphotericin B; VCZ, voriconazole; CAS, caspofungin.

*aNumber of samples is given in parentheses.

*bLevels obtained between 4 and 8 h post-dose.

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### Table 4. Outcome of secondary antifungal prophylaxis at day +180 post-HSCT and long-term follow-up

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Outcome at day +180</th>
<th>Outcome at last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Co-morbidities</td>
<td>response</td>
</tr>
<tr>
<td>1</td>
<td>Died from recurrent leukaemia day +135</td>
<td>possible IPA</td>
</tr>
<tr>
<td>2</td>
<td>Alive</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Alive</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Alive</td>
<td>Recurrent leukaemia day +44 CMV reactivation</td>
</tr>
<tr>
<td>5</td>
<td>Alive</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Alive</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Alive</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>Alive</td>
<td>CMV reactivation, PTLD</td>
</tr>
<tr>
<td>9</td>
<td>Alive</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>Died from graft failure, pneumonia, sepsis day +150</td>
<td>CR</td>
</tr>
<tr>
<td>11</td>
<td>Died from recurrent leukaemia day +125</td>
<td>CR</td>
</tr>
</tbody>
</table>

CR and PR, complete response and partial response of invasive fungal infection; CR-1 and CR-2, first complete and second complete haematological remission; IPA, invasive pulmonary aspergillosis; IA, invasive aspergillosis; CMV, cytomegalovirus; PTLD, post-transplant lymphoproliferative disease; ADV, adenovirus.

*aNote that none of the patients had chronic GVHD.
Discussion

The results of this prospective cohort analysis suggest that administration of LAMB followed by oral voriconazole is a feasible approach to secondary antifungal prophylaxis in paediatric patients with acute leukaemia and a history of possible or probable IPA who are scheduled to undergo allogeneic HSCT. All patients achieved engraftment without evidence for breakthrough infection and were switched to oral voriconazole. At day +180 post-HSCT, the primary endpoint of efficacy, eight patients (73%) were alive, six with complete and one each with near complete and ongoing resolution of pulmonary infiltrates; all but one were in continuing haematological remission. Three patients had succumbed either to recurrent leukaemia or refractory graft failure; one of these patients had maintained a complete response and two patients (18%) died because of secondary possible or probable IPA. Both of these patients had discontinued voriconazole early and developed IPA in lung areas involved during the primary episode. Cognizant of the limitations of such comparisons, the rates of breakthrough fungal infections of 18% at day +180 and of 27% at the last follow-up, respectively, are overall comparable with those reported elsewhere for patients with secondary prophylaxis during AML treatment and allogeneic HSCT.

Important variables inversely associated with recurrent or reactivated invasive aspergillosis include the duration of antifungal therapy prior to HSCT and the resolution of radiographic abnormalities; other factors such as the status of the underlying disease, the type of the conditioning regimen, the duration of granulocytopenia, the presence of GVHD and CMV disease are shared with de novo infections post-HSCT. Whether the secondary or breakthrough infections observed in this and other reported series represent reactivations of the primary infection or de novo infections, and whether they are associated with specific exposure or genetic risk factors, respectively, cannot be determined without appropriate molecular and epidemiological tools. However, the frequent occurrence of secondary infections in previously affected areas and the extended persistence of Aspergillus spp. in lung tissue following recovery of host defences suggest that even late reactivation may be possible. Although selection of resistant A. fumigatus has not yet surfaced as clinical problem, breakthrough infections by zygomycetes have been reported in patients receiving voriconazole and need to be considered as causes of secondary infections in susceptible hosts. The strategy of secondary prophylaxis with iv LAMB followed by oral voriconazole upon engraftment and ability to take oral medication were overall acceptably well tolerated with no serious adverse drug reactions despite prolonged treatment. Whereas LAMB was chosen to cover the initial transplant period from admission until neutrophil engraftment in order to avoid unpredictable drug–drug interactions with anticancer and supportive care medication in a phase of polypharmacotherapy, voriconazole was deemed to have an advantage for long-term administration following engraftment due to its oral availability, despite interactions with calcineurin inhibitors and, potentially, methylprednisolone. LAMB was discontinued early in one patient and voriconazole was transiently or permanently discontinued due to AEs/new contraindications in two patients each. Clinical AEs possibly related to antifungal therapy but not leading to its discontinuation or interruption were minor and few in number. Although increases in renal and hepatic laboratory parameters were seen in all patients during prophylaxis with LAMB and voriconazole, the rate of patients who had such increases to three or more times baseline at the end of therapy was at an acceptable level in both treatment phases. Both frequency and pattern of AEs are in agreement with the experience in other series of secondary prophylaxis in the HSCT setting with LAMB and voriconazole, and with the paediatric experience reported for both agents. Nevertheless, careful clinical and laboratory monitoring is advised with focus on renal function (LAMB) and liver function and drug–drug interactions (voriconazole).

Apart from the limited number of patients, a potential limitation of this series is the question of the validity of diagnoses. The majority of the patients in previous series had either proven or probable aspergillosis based on the EORTC/MSG criteria, whereas 4 of the 11 patients in our series were classified as having possible and 7 as probable invasive aspergillosis on the basis of less stringent criteria used in large randomized Phase III clinical trials. This fact may bias the observed outcome, as higher rates of antifungal treatment failure have been reported in patients with proven as opposed to probable or possible disease. However, the series presented here may not be confounded with an interventional clinical trial. The main purpose of our work was to evaluate the feasibility of a uniform strategy for patients presenting with a history of presumed or proven invasive aspergillosis prior to allogeneic HSCT that reflects clinical practice and that may serve as guidance to clinicians facing the challenges of managing these patients. Nevertheless, the issue of diagnostic validity needs to be considered when interpreting the outcome data of this analysis.

In conclusion, the results of this series support the notion that secondary antifungal prophylaxis for possible or probable IPA can be safely and effectively achieved during and following HSCT using standard agents with a broad-spectrum antifungal activity. In the absence of chronic GVHD, breakthrough infection appeared to be associated with recurrent leukaemia/graft failure, a shorter duration of post-engraftment secondary prophylaxis in comparison with patients without breakthrough infection, and occurrence of the pulmonary infection in a lung area that had been affected during the primary episode.

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Transparency declarations

A. H. G. has served as a consultant to Gilead Sciences, Martinsried, Germany. H. K. and A. H. G. have served as...
Secondary antifungal prophylaxis

clinical investigators for Pfizer Pharmaceuticals, Sandwich, Kent, UK. All other authors: none to declare.

Supplementary data

Table S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


