Aspergilloso invasiva

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The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study

Pagano et al. Haematologica 2006;91:1068-75

1999-2003; 11,802 pts from 18 centers

**Table 1.** Incidence of mold and yeast infections in patients with different types of hematologic malignancies.

<table>
<thead>
<tr>
<th>HM</th>
<th>No. of patients</th>
<th>No. of IF (incidence)</th>
<th>Molds</th>
<th>Yeasts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Incidence %</td>
<td>No. cases</td>
<td>Incidence %</td>
</tr>
<tr>
<td>AML</td>
<td>3012</td>
<td>373 (12%)</td>
<td>239</td>
<td>7.9</td>
</tr>
<tr>
<td>ALL</td>
<td>1173</td>
<td>77 (6.5%)</td>
<td>51</td>
<td>4.3</td>
</tr>
<tr>
<td>CML</td>
<td>596</td>
<td>15 (2.5%)</td>
<td>14</td>
<td>2.3</td>
</tr>
<tr>
<td>CLL</td>
<td>1104</td>
<td>6 (0.5%)</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>NHL</td>
<td>3457</td>
<td>54 (1.6%)</td>
<td>30</td>
<td>0.9</td>
</tr>
<tr>
<td>HD</td>
<td>844</td>
<td>6 (0.7%)</td>
<td>3</td>
<td>0.35</td>
</tr>
<tr>
<td>MM</td>
<td>1616</td>
<td>7 (0.5%)</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>Total</td>
<td>11802</td>
<td>538 (4.6%)</td>
<td>346</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**Table 2.** Species distribution of invasive fungal infections in patients with hematologic malignancies.

<table>
<thead>
<tr>
<th>Infections caused by</th>
<th>No. of cases (%)</th>
<th>Incidence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molds</td>
<td><strong>346 (100)</strong></td>
<td><strong>2.9</strong></td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>310 (90)</td>
<td>2.6</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>14 (4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Fusarium spp.</td>
<td>15 (4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Others *</td>
<td>7 (2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Yeasts</td>
<td><strong>192 (100)</strong></td>
<td><strong>1.6</strong></td>
</tr>
<tr>
<td>Candida spp.</td>
<td>175 (91)</td>
<td>1.5</td>
</tr>
<tr>
<td>Cryptococcus spp.</td>
<td>8 (4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Trichosporon spp.</td>
<td>7 (4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Others °</td>
<td>2 (1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
There were 619,702 inpatient-episodes among 32,815 HM and 1,765 HSCT-patients. IFD occurring twelve months from HM-diagnosis was detected in 669 (2.04%) HM-patients and 111 (6.29%) HSCT-recipients, respectively.
A population-based analysis of invasive fungal disease in haematology-oncology patients using data linkage of state-wide registries and administrative databases: 2005 - 2016

A population-based analysis of invasive fungal disease in haematology-oncology patients using data linkage of state-wide registries and administrative databases: 2005 - 2016

Jake C. Valentine, C. O’Hea Monksley, Mark A. Tacey, Danny Liu, Suchrit Patil, Anton Y. Peleg and Michelle R. Ananda-Rajah
A population-based analysis of invasive fungal disease in haematology-oncology patients using data linkage of state-wide registries and administrative databases: 2005 - 2016

 Jake C. Valentine¹,², C. Oda Montrey³, Mark A. Tacey⁴, Danny Law⁵, Sudhir Pati⁶, Anton Y. Peleg⁷ and Michelle R. Ananda-Taylor⁷

Fig. 4 Kaplan-Meier survival curves illustrating overall survival (months) from invasive fungal disease diagnosis between invasive aspergillosis (IA), invasive candidiasis (IC), mucormycosis and other invasive fungal disease. IFD, invasive fungal disease.

<table>
<thead>
<tr>
<th>Drug used in prophylaxis (n. of courses)</th>
<th>% of proven-probable breakthrough IFDs (range)</th>
<th>% of proven-probable breakthrough IA (range)</th>
<th>% of proven-probable breakthrough IC (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole (843)</td>
<td>6.4 (3.8 - 14)</td>
<td>4.5 (0 - 9.7)</td>
<td>1.2 (0 – 2.5)</td>
</tr>
<tr>
<td>Posaconazole (2149)</td>
<td>4.8 (0 - 23.2)</td>
<td>3.3 (0 - 15.1)</td>
<td>0.9 (0 – 9)</td>
</tr>
<tr>
<td>Voriconazole (431)</td>
<td>3.2 (0 – 6.6)</td>
<td>2.1 (0 – 2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Total (3423)</td>
<td>5.2</td>
<td>3.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

IFD: invasive fungal disease; IA: invasive aspergillosis; IC: invasive candidosis
Of 2588 patients in complete remission after induction therapy and therefore submitted to consolidation, 56 (2.2%) developed IA.

Delivering AP in consolidation was associated with a significant benefit. In fact, the diagnosis of IA was made in 34 of 1137 (2.9%) patients who did not receive AP and in 22 of 1451 who did receive it (1.5%) (P=0.01).

The number needed to treat to achieve one additional patient who will benefit from the AP was 71.

Further prospective studies should be carried out particularly in elderly patients treated with high-dose cytarabine to confirm our data and to identify subsets of individuals who may require AP.
Long-Lasting Protective Effect of Posaconazole Prophylaxis in Patients with Acute Myeloid Leukemia Receiving Allogeneic Hematopoietic Stem Cell Transplantation

Alessandro Busca 1, Anna Cardoni 1, Ernesta Audisio 1, Roberto Passera 1, Benedetto Bruno 1, Federico Monaco 1, Nicola Medini 1, Adriana Vacca 1, Mario Dellia 1, Franco Aversa 1, Livio Pagano 1

*Figure 1. Flow diagram outlining patients' enrollment into the study protocol.*

*Figure 2. Cumulative incidence of IFI in AML patients submitted to allogeneic HSCT after receiving fluconazole/itraconazole (dashed line) or posaconazole (solid line) prophylaxis during induction/salvage chemotherapy (P = 0.012).*

*Figure 3. Fungal-free survival of AML patients submitted to allogeneic HSCT after receiving fluconazole/itraconazole (dashed line) or posaconazole (solid line) prophylaxis during induction/salvage chemotherapy (P = 0.135).*
<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Time interval from chemotherapy to HSCT</td>
<td>.54 (.22-1.35)</td>
<td>.191</td>
</tr>
<tr>
<td>Disease phase of AML</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Savage versus induction</td>
<td>1.54 (.61-3.87)</td>
<td>.358</td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUD versus MSD</td>
<td>3.25 (1.13-9.39)</td>
<td>.029</td>
</tr>
<tr>
<td>Haplo/PMRD versus MSD</td>
<td>3.19 (.70-14.48)</td>
<td>.133</td>
</tr>
<tr>
<td>Status at HSCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse versus CR</td>
<td>1.61 (.55-4.67)</td>
<td>.382</td>
</tr>
<tr>
<td>Stem cell source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBSC versus BM</td>
<td>.52 (.17-1.59)</td>
<td>.248</td>
</tr>
<tr>
<td>Conditioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIC versus MAC</td>
<td>4.92 (1.95-12.39)</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Antifungal prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itra/fluco versus posa</td>
<td>3.82 (1.25-11.67)</td>
<td><strong>.019</strong></td>
</tr>
</tbody>
</table>

Bold indicates statistical significance.
MSD indicates matched sibling donor; Haplo, haploidentical; MSD, matched sibling donor; Itra, itraconazole; fluco, fluconazole; posa, posaconazole.
Interactions of antimicrobials with FLT-3 inhibitors
Pharmacokinetic data

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP3A4</th>
<th>P-gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midostaurin</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>S</td>
<td>inhib</td>
</tr>
</tbody>
</table>

- **Strong CYP3A4 inhibitors:** clarithromycin, itraconazole, ketoconazole, voriconazole, posaconazole
- **Moderate CYP3A4 inhibitors:** ciprofloxacin, levofloxacin, fluconazole, erythromycin
- **Weak CYP3A4 inhibitors:** isoniazid, azithromycin, metronidazole, caspofungin, isavuconazole
- **Strong/moderate CYP2C9 inhibitors:** fluconazole
- **P-gp inhibitors:** itraconazole, posaconazole, clarithromycin, erythromycin, ofloxacin, levofloxacin

Ketoconazole interaction in healthy subjects:
- Midostaurin: increased $C_{max}$ 1.8 fold, AUC $0-\infty$ 10 fold
- Sorafenib: no interaction observed

Rifampin interaction in healthy subjects
- Midostaurin: decreased $C_{max}$ 4 fold, AUC $0-\infty$ 13 fold
- Sorafenib: 37% reduction of the AUC

Clinical implications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Co-dministration with strong CYP3A4 inhibitors</th>
<th>Co-dministration with moderate CYP3A4 inhibitors</th>
<th>Co-dministration with weak CYP3A4 inhibitors</th>
<th>Co-dministration with CYP3A4 inducers</th>
<th>Co-dministration with P-gp inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midostaurin</td>
<td>Avoid</td>
<td>Avoid</td>
<td>???</td>
<td>Avoid</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>No implication</td>
<td>No implication</td>
<td>No implication</td>
<td>No implication</td>
<td>Dose adjustment??</td>
</tr>
</tbody>
</table>
There were 619,702 inpatient-episodes among 32,815 HM and 1,765 HSCT-patients. IFD occurring twelve months from HM-diagnosis was detected in 669 (2.04%) HM-patients and 111 (6.29%) HSCT-recipients, respectively.

Table 2: Invasive Fungal Disease Incidence Stratified by Haematological Malignancy and Haematopoietic Stem Cell Transplantation from Index Hospitalisation, 2005 - 2016

<table>
<thead>
<tr>
<th>Haematological malignancy and haematopoietic stem cell transplantation</th>
<th>Invasive fungal disease; incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic-haematopoietic stem cell transplantation (N = 335)</td>
<td>41 (12.2)</td>
</tr>
<tr>
<td>Acute lymphoblastic leukaemia (N = 664)</td>
<td>75 (11)</td>
</tr>
<tr>
<td>Acute myeloid leukaemia (N = 2,644)</td>
<td>249 (9.42)</td>
</tr>
<tr>
<td>Autologous-haematopoietic stem cell transplantation (N = 1,449)</td>
<td>70 (48.3)</td>
</tr>
<tr>
<td>Aplastic anaemia (N = 7,121)</td>
<td>101 (1.42)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukaemia (N = 3,459)</td>
<td>46 (13.3)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma (N = 15,267)</td>
<td>192 (1.26)</td>
</tr>
<tr>
<td>Multiple myeloma (N = 5,614)</td>
<td>58 (1.03)</td>
</tr>
<tr>
<td>Hodgkin lymphoma (N = 2,030)</td>
<td>17 (0.84)</td>
</tr>
<tr>
<td>Chronic myeloid leukaemia (N = 1,240)</td>
<td>10 (0.81)</td>
</tr>
<tr>
<td>Other haematological malignancies (N = 1,897)</td>
<td>22 (1.16)</td>
</tr>
</tbody>
</table>

*Myelodysplastic syndrome patients included in ‘Other’ due to a small patient cohort.
Current strategies in the management of hematological diseases in adults

- Acute leukemias intensive chemotherapy
- Stem cell transplants
- Other intensive treatments
- Complications of outpatients

- Acute leukemias post chemotherapy
- Stem cell transplants after engraftment
- Acute leukemias elderly
- MDS
- CML
- CLL
- NHL
- HL
- MM
- Anemias
- Thrombocytopenias
- Neutropenias
- Hemorragic diseases
- Inherited bleeding disorders
- Trombotic disorders
- Several other diseases and conditions
I numeri in un centro di ematologia

Leucemie acute vs emopatie oncologiche non acute

nuove diagnosi:
1:8

pazienti seguiti con malattia attiva:
1:25
Survival of patients with Acute Myeloid Leukemia, Myeloma and non-Hodgkin’s lymphoma according to time period

Projected relative 5-year survival in AML according to age and time period

Non-Hodgkin Lymphoma (C82-C85): 1971-2011
Age-Standardised Ten-Year Net Survival, England and Wales
New drugs and innovative strategies in the treatment of outpatients with hematologic diseases

**Chronic lymphoproliferative diseases**
- Ibrutinib
- Idelalisib
- Venetoclax
- Pomalidomide
- Panobinostat

**Chronic myeloproliferative diseases**
- Bcr-abl TKIs (bosutinib, ponatinib)
- JAC-2 inhibitors (ruxolitinib)

**Acute leukemias and myelodysplastic syndromes**
- FLT3 inhibitors (midostaurin, sorafenib, quizartinib)
- Hypomethylating agents (azacitidine, decitabine)
- Bcr-abl TKIs
The effect of new treatment strategies on some chronic hematologic diseases

- New II, III, IV ...line treatments
- Prolonged survival (generally PFS)
- Increasing prevalence of outpatients surviving with the disease
- Prolonged infectious risk
- Recurrent infections during treatment
- Recent literature data show the emerging risk for invasive aspergillosis in certain populations
<table>
<thead>
<tr>
<th>Disease</th>
<th>ECIL 5 recommendation</th>
</tr>
</thead>
</table>
| ALL          | • there is currently no approved standard of care for patients with ALL  
• against the use of mould-active azoles because of potentially hazardous neurotoxic interactions with Vinca alkaloids  
• in the absence of convincing efficacy and toxicity data, caution use of fluconazole prophylaxis to prevent yeast infections may be considered (C-III).                                                                                     |
| Chronic MPNs | • there is no increased risk of IFD in patients with CML treated with tyrosine kinase inhibitors (TKIs) or in other conventionally treated MPN patients. Primary antifungal prophylaxis is therefore not recommended.                                                                                       |
| MDSs         | • ECIL does not recommend primary antifungal prophylaxis in patients with MDS (excluding those patients undergoing intensive AML-like induction and/or allogeneic HSCT) as they have a low risk (<2%) of IFD.  
• moreover, they typically have prolonged neutropenia for months and even years; this would imply a very prolonged prophylaxis, a situation that has been associated with an increased risk of acquired antifungal resistance. |
<table>
<thead>
<tr>
<th>Disease</th>
<th>ECIL 5 recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Myeloma</td>
<td>• the overall incidence of IFD is low (&lt;2%) consequently, pending further epidemiological data, primary antifungal <strong>prophylaxis is not recommended</strong> for patients being treated for myeloma.</td>
</tr>
<tr>
<td>CLL</td>
<td>• most patients develop bacterial or viral infections rather than IFD and epidemiological data on fungal infections (excluding P. jirovecii) are scarce.</td>
</tr>
<tr>
<td></td>
<td>• <strong>primary antifungal prophylaxis is not recommended</strong>, although it might be considered for patients with prolonged neutropenia, elderly patients and those with advanced and unresponsive CLL disease</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>• Patients with lymphoma tend to be at low risk of IFD therefore <strong>primary antifungal prophylaxis is not recommended</strong></td>
</tr>
</tbody>
</table>
Therapies | Indication for prophylaxis
---|---
**BCR-ABL tyrosine kinase inhibitors: imatinib, dasatinib, nilotinib, bosutinib and ponatinib** |  
• Antiviral prophylaxis while on therapy in HBsAg-positive patients. Monitoring for HBV virus load in anti-HBc positive, HBsAg-negative patients.  
• No expected benefit from universal use of antibacterial, antiviral or anti-Pneumocystis prophylaxis

**Ibrutinib, acalabrutinib** |  
• Modest increase in risk of infection  
• No expected benefit from universal use of antibacterial or antifungal prophylaxis  
• Anti-Pneumocystis prophylaxis for CLL patients with additional risk factors (e.g. purine analogues or high-dose corticosteroids)

**Idelalisib** |  
• Increased risk of OIs and life-threatening adverse events  
• Anti-Pneumocystis prophylaxis during course of therapy and for 2 to 6 months after discontinuation  
• Monitoring for CMV infection during course of therapy in CMV seropositive patients or in presence of suspected CMV disease  
• Discontinuation of therapy in presence of suspected pneumonitis or grade 3/4 aminotransferase elevation or diarrhoea/colitis

**Venetoclax** |  
• No apparent increase in risk of infection
Is primary antifungal prophylaxis indicated in patients with conditions other than AML and allo-SCT?

- The risk of IFD is generally low.
- The period of presumed infectious risk is prolonged
- In these populations a diagnostic-driven approach seems more appropriate

CONSEQUENTLY
- A prophylaxis along the entire treatment period is not indicated

BUT
- Can we consider prophylaxis during a short crucial period?
Patterns of Infection in Patients With Myelodysplastic Syndromes and Acute Myeloid Leukemia Receiving Azacitidine as Salvage Therapy. Implications for Primary Antifungal Prophylaxis

Jose F. Falantes,1 Cristina Calderón,1 Francisco J. Márquez-Malaver,1 Manuela Aguilar-Guisado,2 Almudena Martín-Peña,2 María L. Martíno,4 Isabel Montero,1 Jose González,1 Rocío Parody,1 Jose A. Pérez-Simón,1 Ildefonso Espigado1

Figure 1. Incidence of Febrile Episodes in Each Course of Azacitidine
884 AZA cycles in 68 patients

Figure 2. Incidence of microbiologically-defined infections in patients treated with azacitidine and no prior chemotherapy exposure. AZA: azacitidine.
The total number of AZA cycles was 988, with a median of 8 cycles per patient (range 1 – 56 cycles). There were 41 episodes of lung infection documented by chest CT in 32 patients (37.2% of patients and 4.1% of AZA cycles). Based on the above diagnostic work-up, pulmonary infiltrates were considered of fungal origin in 9 cases (21.9%), associated to bacteremia in 3 cases (7.3%) and of unknown origin in the remaining 29 cases (70.7%). The time of occurrence of lung infections is shown in the Figure. Overall, a pulmonary fungal disease was documented in 6 of 165 (3.6%) cycles 1-2, in 1 of 196 (0.5%) cycles 3-5 and in 2 of 627 (0.3%) cycles since cycle 6 (p=0.001).

Out of 32 patients who developed a pulmonary infection 25 (78%) interrupted the AZA treatment within 3 months from the infectious episode due to deterioration of clinical conditions, hematologic disease progression and/or death, including 8 of 9 (89%) patients who developed a pulmonary fungal disease.

The median overall survival of the whole cohort of patients from AZA start was 16.4 months (IQR 6.8 – 30.9). The median overall survival of patients without pulmonary infections was 21.4 months (IQR 11.9 – 35.1) compared with 9.6 months (IQR 5.9 – 17.2) in patients with pulmonary infection (p=0.001), as shown in the Figure.
**Prevention of infection in MDS patients**

<table>
<thead>
<tr>
<th></th>
<th>LR supportive care</th>
<th>LR Lenalidomide</th>
<th>IR-HR HMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S.pneumoniae vaccination</strong></td>
<td>YES at onset of disease</td>
<td>YES at onset of disease</td>
<td>YES at onset of disease</td>
</tr>
<tr>
<td><strong>Influenza vaccination</strong></td>
<td>YES annually</td>
<td>YES annually</td>
<td>YES annually</td>
</tr>
<tr>
<td><strong>Antibacterial prophylaxis</strong></td>
<td>NO</td>
<td>NO</td>
<td>Consider in the first months</td>
</tr>
<tr>
<td><strong>Mould-active antif. prophylaxis</strong></td>
<td>NO</td>
<td>NO</td>
<td>Consider in the first months</td>
</tr>
<tr>
<td><strong>Anti-herpetic prophylaxis</strong></td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Chronic HBV inf. (HBsAg +, HBV-DNA +)</strong></td>
<td>As in immunocompetent</td>
<td>Tenofovir, entecavir</td>
<td>Tenofovir, entecavir</td>
</tr>
<tr>
<td><strong>Resolved HBV inf. (Anti HBc-Ag +)</strong></td>
<td>As in immunocompetent</td>
<td>Monitoring of seroreversion and/or viremic rebound</td>
<td>Monitoring of seroreversion and/or viremic rebound</td>
</tr>
</tbody>
</table>
Serious Infections in Patients Receiving Ibrutinib for Treatment of Lymphoid Cancer

Tilly Vannaghon, Ying Tuo,1,2 Nina Cohen,3,6 M. Cia Polomski,3,7 Susan K. S. Sun,1,7 Tobias M. Hecht,5,8 and Gil Reidelman-Saad1,2

1Infectious Diseases Service, Memorial Sloan Kettering Cancer Center, Department of Medicine, Weill Cornell Medical College, and Department of Neuroscience and 2Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, New York

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![Graph showing proportion of infection with time after Ibrutinib initiation.]

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Table 4. Infection Risk Analysis: Patients With Versus Patients Without Invasive Fungal Infection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.002 (.96–1.05)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.46 (.13–1.58)</td>
</tr>
<tr>
<td>CLL as underlying cancer</td>
<td>1.78 (.66–4.83)</td>
</tr>
<tr>
<td>Ibrutinib daily dose</td>
<td>1.00 (.996–1.004)</td>
</tr>
<tr>
<td>≥3 Prior treatment regimens</td>
<td>3.35 (1.22–9.21)</td>
</tr>
<tr>
<td>Concurrent antitumor agents other than ibrutinib</td>
<td>2.33 (.74 – 7.31)</td>
</tr>
<tr>
<td>Prior fludarabine</td>
<td>1.34 (.29–5.41)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2.92 (1.71–12.09)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>3.36 (.98–11.55)</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>4.29 (1.40–13.18)</td>
</tr>
<tr>
<td>Antimicrobial prophylaxis</td>
<td></td>
</tr>
<tr>
<td>PJP prophylaxis</td>
<td>1.63 (.47–5.66)</td>
</tr>
<tr>
<td>Antifungal prophylaxis</td>
<td>2.12 (.28–15.91)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; OR, odds ratio; PJP, Pneumocystis jirovecii pneumonia.
Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib

Increased risk of IFI was not apparent in the results of the initial clinical studies on ibrutinib in CLL. Our results and that of others confirm that ibrutinib may be associated with IFI in real life.

Although it seems difficult at this point to advocate for systematic antifungal prophylaxis in all patients, an increased awareness about the potential risk of IFI after initiating ibrutinib is warranted, especially when other predisposing factors are associated.

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Number of patients (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
</tr>
<tr>
<td>Median [range]</td>
<td>70 [31-82]</td>
</tr>
<tr>
<td><strong>Number of previous lines of treatment</strong></td>
<td>2 [0-4]</td>
</tr>
<tr>
<td><strong>17p deletions</strong></td>
<td>15/30 CLL</td>
</tr>
<tr>
<td><strong>Interval between last line and ibrutinib (months)</strong></td>
<td>10.5 [1-96]</td>
</tr>
<tr>
<td><strong>Hypogammaglobulinemia</strong></td>
<td></td>
</tr>
<tr>
<td>Yes [intravenous immunoglobulins substitution]</td>
<td>31 [8]</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td><strong>Additional predisposing factors for IFI</strong></td>
<td></td>
</tr>
<tr>
<td>Neutropenia [grade 4]</td>
<td>5 [2]</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>4</td>
</tr>
<tr>
<td>Rituimab + corticosteroids</td>
<td>3</td>
</tr>
<tr>
<td>Rituimab</td>
<td>2</td>
</tr>
<tr>
<td>Concomitant immunotherapy</td>
<td>3</td>
</tr>
<tr>
<td>Chemotherapy ≤6 mo</td>
<td>10</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1</td>
</tr>
<tr>
<td>HIV</td>
<td>1</td>
</tr>
</tbody>
</table>

**Characteristics of invasive fungal infection**

<table>
<thead>
<tr>
<th>Isolated microorganism</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus fumigatus</td>
<td>16</td>
</tr>
<tr>
<td>Aspergillus nidulans</td>
<td>1</td>
</tr>
<tr>
<td>Zygomyces (Lichtheimia corymbifera)</td>
<td>1</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>3</td>
</tr>
<tr>
<td>Pneumocystis jirovecii</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive at last follow-up</td>
<td>16</td>
</tr>
<tr>
<td>Death</td>
<td>17</td>
</tr>
<tr>
<td>Because of IFI</td>
<td>9</td>
</tr>
<tr>
<td>Because of CLL</td>
<td>5</td>
</tr>
<tr>
<td>Other causes</td>
<td>3</td>
</tr>
</tbody>
</table>
Btk is required for the macrophage inflammatory response that clears *A fumigatus* from the airways.
Group A: not significant dose reduction
Group B: any dose reductions but no treatment breaks greater than 14 days
Group C: ibrutinib was withheld for longer than 14 days, either temporarily or permanently
CLL, ibrutinib and invasive Aspergillosis

- Invasive Aspergillosis is a life threatening complication
- Ibrutinib therapy should be discontinued until an appropriate infection control is achieved
- Prolonged discontinuation of ibrutinib therapy may be associated with a progression of CLL and reduced overall survival probability

May primary anti-Aspergillus prophylaxis be indicated in certain patients during a certain period?
CYP450 metabolism and possible drug-drug interactions of certain molecules used in hematology

- **CYP1A2**: Bortezomib, pomalidomide
- **CYP2C9**: Cyclophosphamide, Idarubicin, Bortezomib
- **CYP2C19**: Bortezomib
- **CYP3A4**: Cyclophosphamide, busulfan, thiotepa, vinca alcaloids, etoposide, daunorubicin, bortezomib, BCR-ABL TKIs, ibrutinib, idelalisib, venetoclax, pomalidomide, panobinostat, calcineurin inhibitors.

Drugs generally used in outpatient regimens
CLL, ibrutinib and invasive Aspergillosis

We can:
1. Start voriconazole and stop ibrutinib
2. Start voriconazole and reduce ibrutinib dose
3. Start isavuconazole, continue full dose ibrutinib, use ibrutinib TDM
Drug-drug interactions of triazoles in hematology

CYP-2C9 substrates
- Cyclophosphamide
- Idarubicin

CYP-2C19 substrates
- Bortezomib

CYP-3A4 substrates
- Cyclophosphamide
- Busulfan, Thiotepa
- Vinca alkaloids, Etoposide
- Daunorubicin
- Bortezomib
- BCR-ABL TKIs
- Ibrutinib, Idelalisib, Venetoclax
- Calcineurin inhibitors

Severe inhibition
Moderate inhibition
Mild inhibition
Interactions of antimicrobials with Ibrutinib, Idelalisib, Venetoclax

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP3A4</th>
<th>P-gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>S</td>
<td>Inhib</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>S Inhib</td>
<td></td>
</tr>
<tr>
<td>Venetoclax</td>
<td>S Inhib</td>
<td>S</td>
</tr>
</tbody>
</table>

Ketoconazole interaction in healthy subjects:
- Ibrutinib: increased $C_{\text{max}}$ 29 fold, $AUC_{0-\infty}$ 24 fold
- Idelalisib: increased $C_{\text{max}}$ 1.8 fold, $AUC_{0-\infty}$ 4.8 fold
- Venetoclax: increased $C_{\text{max}}$ 2.3 fold, $AUC_{0-\infty}$ 6.4 fold

Clarithromycin interaction in healthy subjects:
- Ibrutinib: increased $AUC_{0-\infty}$ 14 fold

Rifampin interaction in healthy subjects:
- Ibrutinib: decreased $C_{\text{max}}$ 92%, $AUC_{0-\infty}$ 90%
- Idelalisib: decreased $AUC_{0-\infty}$ 82%
- Venetoclax: decreased $AUC_{0-\infty}$ 71%

Clinical implications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Co-administration with strong CYP3A4 inhibitors</th>
<th>Co-administration with moderate CYP3A4 inhibitors</th>
<th>Co-administration with weak CYP3A4 inhibitors</th>
<th>Co-administration with CYP3A4 inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td><strong>Avoid</strong>, if not possible reduce Ibr dosage</td>
<td><strong>Avoid</strong>, if not possible reduce Ibr dosage</td>
<td>No dosage reduction required</td>
<td><strong>Avoid</strong></td>
</tr>
<tr>
<td>Idelalisib</td>
<td>No dosage reduction required</td>
<td>No dosage reduction required</td>
<td>No dosage reduction required</td>
<td><strong>Avoid</strong></td>
</tr>
<tr>
<td>Venetoclax</td>
<td><strong>Avoid</strong>, At steady daily dose reduce Ven by 75%</td>
<td><strong>Avoid</strong>, if not possible reduce Ven dosage by 50%</td>
<td>No dosage reduction required</td>
<td><strong>Avoid</strong></td>
</tr>
</tbody>
</table>
The ibritinib dose should be reduced to 140 mg (quarter of maximal prescribed dose) when coadministered with moderate CYP3A4 inhibitors so that exposures remain within observed ranges at therapeutic doses.
The recommended venetoclax dose reductions of at least 50% and 75% when coadministered with moderate and strong CYP3A inhibitors, respectively, maintain venetoclax exposures between therapeutic and maximally administered safe doses.
CONCLUSIONS The results of this study confirm the major role of CYP3A in the metabolism of venetoclax. Posaconazole can be used for antifungal prophylaxis in AML patients receiving venetoclax after reducing the venetoclax dose by at least 75%.
Infectious complications of CD19-targeted chimeric antigen receptor–modified T-cell immunotherapy

Table 2. Incidence of specific infections through 28 days after CAR-T-cell infusion

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>ALL, n = 47</th>
<th>CLL, n = 24</th>
<th>NHL, n = 62</th>
<th>Total, N = 133</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>No. of patients (%)</td>
<td>Events</td>
<td>No. of patients (%)</td>
</tr>
<tr>
<td>Any infection</td>
<td>21</td>
<td>14 (29.8)</td>
<td>8</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td><strong>Bacterial infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>13</td>
<td>12 (25.5)</td>
<td>4</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Bacterial site infection†</td>
<td>5</td>
<td>5 (10.6)</td>
<td>2</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td><strong>Viral infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory virus‡</td>
<td>6</td>
<td>5 (10.6)</td>
<td>3</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Other virus§</td>
<td>6</td>
<td>5 (10.6)</td>
<td>3</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td><strong>Fungal infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonmold†</td>
<td>2</td>
<td>2 (4.3)</td>
<td>1</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Mold‡</td>
<td>1</td>
<td>1 (2.1)</td>
<td>0</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Table 4. Post-CAR-T-cell infusion factors and risk for first infection within 28 days using Cox proportional hazards regression

<table>
<thead>
<tr>
<th>Post-CAR-T-cell infusion variables</th>
<th>Unadjusted HR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR-T-cell dose level, cells per kg</td>
<td>3.19 (1.07-9.51)</td>
<td>.038</td>
</tr>
<tr>
<td>2 x 10^9 vs 2 x 10^7</td>
<td>3.15 (1.24-8.01)</td>
<td>.016</td>
</tr>
<tr>
<td>ANC &lt; 500 cells per mm^3 on day of infection</td>
<td>2.04 (0.85-4.89)</td>
<td>.11</td>
</tr>
<tr>
<td>C3-C4 grade</td>
<td>3.38 (1.99-5.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0 vs 1-3 vs 4-5†</td>
<td>1.76 (1.11-2.78)</td>
<td>.015</td>
</tr>
<tr>
<td>Neurotoxicity grade</td>
<td>3.45 (1.23-9.67)</td>
<td>.019</td>
</tr>
<tr>
<td>0 vs 1-2 vs 3-5§</td>
<td>1.50 (0.43-5.23)</td>
<td>.5</td>
</tr>
<tr>
<td>ICU admission</td>
<td>4.35 (1.78-10.65)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Figure 1. Cumulative incidence curves of time-to-first infection for any infection and for specific infection categories. (A-D): Cumulative incidence among all patients (n = 133) for any (A), bacterial (B), viral (C), and fungal (D) infections within the first 28 days after CAR-T-cell infusion. Dotted lines represent 95% CIs.
Cytokine Release Syndrome Grade as a Predictive Marker for Infections in Patients With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia Treated With Chimeric Antigen Receptor T Cells

Jan H. Park,1,2,3 F. Andrea Romero,4,1 Ying Tan,1,2 Michel Sadelain,1,2,3 Renier J. Brentjens,1,2,3 Tobias M. Hohl,3,4 and Susan K. Seo2,4

1Lymphoma Service and 2Cell Therapy and Cell Engineering Facility, Memorial Sloan Kettering Cancer Center; 3Department of Medicine, Icahn School of Medicine at Mount Sinai; and 4Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York

Table 3. Comparison of Early Versus Late Infections After Chimeric antigen receptor T-cell infusion

<table>
<thead>
<tr>
<th></th>
<th>Early (Day 0–30) (n = 53)</th>
<th>Late (Day 31–180) (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infections, No.</td>
<td>Patients, No. (%)</td>
</tr>
<tr>
<td>Any infection</td>
<td>26</td>
<td>22 (42)³</td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloodstream⁰</td>
<td>8</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Bacterial site</td>
<td>9</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeast⁰</td>
<td>1</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Mold⁰</td>
<td>3</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory virus</td>
<td>3</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Other virus¹</td>
<td>2</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Figure 2. Cumulative incidence of infection after chimeric antigen receptor T-cell infusion (CTI) and cytokine release syndrome (CRS). A. Cumulative incidence of any infection in patients by CRS grade. B. Cumulative incidence of bloodstream infection by CRS grade. Note that all the analysis was CRS grade 3–4.
Serum Galactomannan–Based Early Detection of Invasive Aspergillosis in Hematology Patients Receiving Effective Antimold Prophylaxis

Table 5. Performance of the Serum Galactomannan Assay in High-Risk Patients Receiving Effective Antimold Prophylaxis

<table>
<thead>
<tr>
<th>Evaluation episode, No.</th>
<th>217</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM test results&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>True positive, No. (%)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>True negative, No. (%)</td>
<td>182 (83.9)</td>
</tr>
<tr>
<td>False positive, No. (%)</td>
<td>30 (13.8)</td>
</tr>
<tr>
<td>False negative</td>
<td></td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>100&lt;sup&gt;c&lt;/sup&gt; 70&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>85.5&lt;sup&gt;c&lt;/sup&gt; 90&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Scenario 1: GM screening of all cases<sup>e</sup>**

| Negative predictive value, % | 100<sup>c</sup> 99.4<sup>d</sup> |
| Positive predictive value, % | 11.8<sup>c</sup> 11.9<sup>d</sup> |

**Scenario 2: Diagnosis of IFD suspicion only<sup>f</sup>**

| Negative predictive value, % | 100<sup>c</sup> 70.6<sup>d</sup> |
| Positive predictive value, % | 89.6<sup>c</sup> 89.7<sup>d</sup> |

Abbreviations: GM, galactomannan; IA, invasive aspergillosis; IFD, invasive fungal disease.

<sup>a</sup> Excluding from the series 39 GM nonevaluable episodes and 6 cases from the GM all negative cohort who died during the episode with no autopsy available to completely rule out IA at patient's death, as described in the text.

<sup>b</sup> Definitions and calculations of the tests results are described in the "Methods" section.

<sup>c</sup> Predictive values, both for scenario 1 and scenario 2, are calculated using the sensitivity and specificity serum GM test values from our series.

<sup>d</sup> Predictive values, both for scenario 1 and scenario 2, are calculated using standard reference values for sensitivity and specificity of the assay in high-risk hematology patients obtained from the literature [8, 9].

<sup>e</sup> GM performance when used in a preemptive fashion, including GM surveillance of asymptomatic patients (prevalence of IA: 1.9%).

<sup>f</sup> GM performance in diagnostic-driven use for patients with a clinical suspicion of IFD (prevalence of IA: 55.5%).

Conclusions. The low pretest risk of invasive aspergillosis in the context of effective antimold prophylaxis renders serum GM surveillance of asymptomatic patients unreliable, as all results would be either negative or false positive. The test remains useful to diagnose patients with a clinical suspicion of invasive fungal disease, calling for a more efficient copositioning of effective prophylaxis and GM testing in this clinical setting.
Table 5. Performance of the Serum Galactomannan Assay in High-Risk Patients Receiving Effective Antimold Prophylaxis

<table>
<thead>
<tr>
<th>Evaluation Category</th>
<th>No.</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable episodes</td>
<td>217</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM test results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positive</td>
<td>5 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negative</td>
<td>182 (83.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False positive</td>
<td>30 (13.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100(^c)</td>
<td></td>
<td>70(^d)</td>
</tr>
<tr>
<td>Specificity</td>
<td>85.5(^c)</td>
<td></td>
<td>90(^d)</td>
</tr>
<tr>
<td>Scenario 1: GM screening of all cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>100(^c)</td>
<td>99.4(^d)</td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>11.8(^c)</td>
<td>11.9(^d)</td>
<td></td>
</tr>
<tr>
<td>Scenario 2: Diagnosis of IFD suspicion only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>100(^c)</td>
<td>70.6(^d)</td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>89.6(^c)</td>
<td>89.7(^d)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GM, galactomannan; IA, invasive aspergillosis; IFD, invasive fungal disease.

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Galactomannan kynetic

Neutropenic vs non neutropenic

GM pos

GM neg
The changing epidemiology of invasive aspergillosis in hematologic patients

• Acute leukemia and allogeneic HSCT still continue to be the populations at higher risk for IA despite antifungal prophylaxis

• Overall incidence of IA is still low in other hematological diseases and conditions but the proportion of cases in patients other than AL and HSCT is significant

• Primary antifungal prophylaxis does not seem to be generally indicated but it might be considered in certain disease phases

• Diagnostic strategy of IA should be adapted to the different populations