Aspergillosis

Invasive disease in patients with leukemia

Johan Maertens, MD
Dept of Hematology
University Hospital Gasthuisberg
Catholic University Leuven
Belgium
Invasive fungal infections in patients with hematological malignancies

excluding allogeneic transplantation

Aspergillus 90%
Zygomycetes 4%
Fusarium 4%
Others 2%

Pagano L et al. Haematologica 2006; 91: 1068-1075
Invasive aspergillosis in patients with acute leukemia

Improved Treatment

↑ probable IA GM-PCR-CT

P = .002

Incidence AMR

Risk factors for IA in neutropenic patients with hematologic malignancies

- AML, MDS, ALL
  - Duration of neutropenia
  - Remission-induction chemotherapy
  - Short interval between cycles

- Age
- Gender
- Co-morbidity score
- Relapsed malignancy
- High dose Ara-C (± fludara)

MASCC II
Risk factors IFI in febrile neutropenic patients

Mühlemann et al. Leukemia 2005; 19: 545-550
Pathogenesis of invasive aspergillosis

Neutropenia

Cellular trafficking
BAL fluid

Pathology
Diffuse pneumonia
Few bronchiolitis
No neutrophil infiltration

Fungal development
Invasion by large numbers of hyphae

Chitin
High in all organs

Galactomannan
High

Chamilos et al. Haematologica 2006; 91: 986-9
Issues “specific” to leukemia (→neutropenic) patients

- Hospitalized patients→ screening
- Improvements in rapid and accurate diagnosis of IA
- Paradigm of host immunity→ pIRIS
- Fewer drug interactions
- Co-morbidities
- Surgical intervention
- Prevention or early-diagnosis of IA
- First line therapy
Clinical and radiological predictors of IA in 96 cancer patients

Hachem R et al. Cancer 2006; 106: 1581-1586
Clinical and radiological predictors of IA in 96 cancer patients

Odds ratio for risk of IPA
Multiple Regression Model

- Leukemia: 3.00
- Neutropenia: 4.30
- Cavitary lesions: 10.96
- Nodular lesions: 4.83

Hachem R et al. Cancer 2006; 106: 1581-1586
# Sensitivity of conventional diagnostic procedures

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Procedure</th>
<th>% performed</th>
<th>% sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Chest X-ray</td>
<td>98</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>BAL culture</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Sputum</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Nasal swab</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Surgical specimen</td>
<td>18</td>
<td>87</td>
</tr>
<tr>
<td>Cerebral</td>
<td>Cerebral CT</td>
<td>65</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>Surgical specimen</td>
<td>8</td>
<td>66</td>
</tr>
<tr>
<td>Sino-nasal</td>
<td>Cranial CT</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Nasal swab</td>
<td>71</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Surgical specimen</td>
<td>19</td>
<td>100</td>
</tr>
</tbody>
</table>

*Pagano et al. Haematologica 2001; 86: 862-870*
CT imaging in IA

<table>
<thead>
<tr>
<th>Nodules in IA</th>
<th>Nodule</th>
<th>Nodule with Halo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrop</td>
<td>97 %</td>
<td>82 %</td>
</tr>
<tr>
<td>Non neutrop</td>
<td>96 %</td>
<td>49 %</td>
</tr>
<tr>
<td>Hemato</td>
<td>96 %</td>
<td>49 %</td>
</tr>
<tr>
<td>Non-hemato</td>
<td>82 %</td>
<td>24 %</td>
</tr>
</tbody>
</table>

Greene et al.  
*Clin Infect Dis* 2007; 44: 373-9
## Non-culture based microbiological assays

<table>
<thead>
<tr>
<th></th>
<th>GM</th>
<th>PCR</th>
<th>Glucan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early detection</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Broad range of pathogens</strong></td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Identification to species level</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Good performance</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Quantitative results</strong></td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Rapid available</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Low cost</strong></td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Excellent negative predictive values
Per-test sensitivity & specificity for different cutoffs

Maertens et al. CID 2007; 44: 1329
Neutropenic patients and HSCT recipients
Solid organ transplant recipients and ICU patients

Blood samples-2x/week-OD index ≥0.5 (caveats!)

Outcome and Prognosis?
SCREENING

BAL but OD index unknown

Outcome and Prognosis?
DIAGNOSIS

Serum?
Negative and positive predictive value in neutropenia

Presumptive treatment for IA in allogeneic HSCT recipients (before engraftment)

- 73 FN > 7 days
- 13 empirical
  - 0 IA
- 60 presumptive
  - 56 no antifungal
    - 1 IA
  - 4 antifungal
    - 1 IA

IA-related mortality 0%

Fluconazole 200 mg/d GM and β-D-glucan/wk Nodules on X-ray/CT EORTC-MSG def

Oshima K et al. J Antimicrobial Chemother 2007
Fluconazole prophylaxis

Persistent neutropenic FUO ≥ 4 day while receiving appropriate AB therapy

GAPS IN KNOWLEDGE
Safe and effective to continue fluconazole prophylaxis with negative chest CT findings and laboratory markers??

STANDARD OF CARE
Empirical modification of antifungal regimen to a mold-active agent

‘PIRIS’
Pulmonary Immune Reconstitution Inflammatory Syndrome

- Neutrophils: 0/µL
- Neutrophils: 12.360 /µL
- GM serum: 3.2
- GM serum: 0.8
- GM BAL: 8.6
- GM BAL: 1.2

Caspofungin 70/50
‘PIRIS’

Pulmonary Immune Reconstitution Inflammatory Syndrome

- New onset of or worsening clinical and radiological pulmonary findings consistent with an infectious/inflammatory pulmonary condition
- Temporal relationship with neutrophil recovery
- Absence of new extrapulmonary lesions
- ≥ 50% decrease in serum GMI titers without treatment modifications
- Subsequent resolution without treatment modification

GM index as a surrogate endpoint for outcome of invasive aspergillosis

- 43 patients with IA (89% myeloma)
- Correlation between clinical outcome (survival or death) and GMI-based outcome (kappa correlation)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Assessment</th>
<th>&quot;good&quot;</th>
<th>excellent</th>
<th>perfect</th>
</tr>
</thead>
<tbody>
<tr>
<td>From start of anti-mold therapy</td>
<td>6 weeks</td>
<td>0.74</td>
<td>0.94</td>
<td>1.0</td>
</tr>
<tr>
<td>From first (+) GMI</td>
<td>9 weeks</td>
<td>0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary treatment of invasive aspergillosis in ‘leukemia’


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampho B</td>
<td>38%</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>63%</td>
</tr>
<tr>
<td>AmBisome</td>
<td>49%</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>33%</td>
</tr>
</tbody>
</table>
Primary treatment of invasive aspergillosis in ‘leukemia’


<table>
<thead>
<tr>
<th>Study</th>
<th>Vorico</th>
<th>L-AmB 3</th>
<th>Caspo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological malignancy</td>
<td>52.1%</td>
<td>93%</td>
<td>100%</td>
</tr>
<tr>
<td>Microbiologically confirmed</td>
<td>68.1%</td>
<td>38%</td>
<td>100%</td>
</tr>
<tr>
<td>Antigen only</td>
<td>-</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Survival @ w12</td>
<td>70.8%</td>
<td>72%</td>
<td>54%</td>
</tr>
<tr>
<td>Success @ end of therapy</td>
<td>53.5%</td>
<td>50%</td>
<td>33%</td>
</tr>
<tr>
<td>Neutropenia @ baseline</td>
<td>45%*</td>
<td>71%</td>
<td>85%</td>
</tr>
<tr>
<td>Success in neutropenia @ baseline</td>
<td>50.8%</td>
<td>43%</td>
<td>29%</td>
</tr>
</tbody>
</table>
Patients with uncontrolled malignancy have a lower survival at 12 weeks

- **Heme Malignancy (all):**
  - Uncontrolled Malignancy: 54%
  - Controlled Malignancy: 81%
  - P < .001

- **Leukemias (all):**
  - Uncontrolled Malignancy: 57%
  - Controlled Malignancy: 82%
  - P = .004

- **Acute Leukemias:**
  - Uncontrolled Malignancy: 63%
  - Controlled Malignancy: 82%
  - P = .027

- **Lymphomas:**
  - Uncontrolled Malignancy: 41%
  - Controlled Malignancy: 100%
  - P < .001

*OA Cornely, et al. 2nd Advances Against Aspergillosis, Athens, Greece, 2006*
Antifungal Prophylaxis in Cancer Patients: Fluco v. Drug with Antimold Activity: Meta-analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fluco</th>
<th>Anti-mold</th>
<th>Relative risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>248/1697</td>
<td>244/1717</td>
<td>1.14</td>
</tr>
<tr>
<td>Fungal-related mortality</td>
<td>49/1686</td>
<td>32/1656</td>
<td>1.58</td>
</tr>
<tr>
<td>Documented IFI</td>
<td>53/1141</td>
<td>41/1157</td>
<td>1.40</td>
</tr>
<tr>
<td>Any IFI</td>
<td>237/1870</td>
<td>175/1950</td>
<td>1.53</td>
</tr>
<tr>
<td>Documented non-albicans Candida</td>
<td>23/1668</td>
<td>20/1700</td>
<td>1.20</td>
</tr>
<tr>
<td>Documented Aspergillus</td>
<td>83/1913</td>
<td>43/1947</td>
<td>2.13</td>
</tr>
</tbody>
</table>

* Relative risk > 1 favors the anti-mold group

Prophylaxis in leukemia patients: ECIL recommendations

- ANC (cells/mm³)
  - 500

- Chemotherapy/Autologous transpl.

- HSCT
  - Pre-engraftment
  - Engraftment

- GVHD + Immunosuppressive Therapy

- Posaconazole: AI

- Fluconazole: CI

- Itraconazole Os: CI
Conclusions

- IA: an emerging fungal infection in leukemia patients
- IA: improved outcome
- Better diagnostic tools ~ new treatment strategies
- Immune reconstitution
- GM can serve as a surrogate marker
- First line treatment: voriconazole but more data (all agents) would be welcome