Invasive Aspergillosis in Acute Leukaemia

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INVASIVE ASPERGILLOSIS IN VARIOUS CATEGORIES

Cornet et al, J Hosp Infect 2002
### Invasive Aspergillosis in Various Categories

<table>
<thead>
<tr>
<th>Procedure</th>
<th>( \text{# cases} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogenic HSCT</td>
<td>199</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>130</td>
</tr>
<tr>
<td>Acute lymphoid leukemia</td>
<td>63</td>
</tr>
<tr>
<td>Autologous HSCT</td>
<td>24</td>
</tr>
<tr>
<td>Heart-lung transplant</td>
<td>8</td>
</tr>
<tr>
<td>Small bowel ± liver transplant</td>
<td>3</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>2</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>29</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>10</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>10</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>57</td>
</tr>
</tbody>
</table>

*NOT ALL PATIENTS ARE AT THE SAME RISK!!*

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*Cornet et al, J Hosp Infect 2002*
SEIFEM-2004 Study

11,802 patients
538 IFIs

18 Haematology Divisions

Pagano et al, Haematologica 2006

Underlying diseases

- AML 26%
- MM 14%
- ALL 10%
- CML 5%
- CLL 9%
- NHL 29%
- HL 7%
**INVASIVE FUNGAL INFECTIONS**

- **Aspergillus spp**: 310 cases (58%)
- **Candida spp**: 175 cases
- **Other moulds**: 28 cases
- **Other yeasts**: 15 cases

Total Invades Fungal Infection (IFIs): 538 cases

*Pagano et al, Haematologica 2006*
INVASIVE ASPERGILLOSIS

AML:
EPISODES 213/310
INCIDENCE 7,1%

NOT ALL HAEMATOLOGICAL PATIENTS ARE AT THE SAME RISK !!!

Pagano et al, Haematologica 2006
ASPERGILLOSIS IN AML versus ALLOGENIC-HSCT

Caira et al, Eur J Haematol 2008

Incidence

10.9% Vs 6.3%; p<0.001

9 Italian centres
1999-2003

Cases
Moulds

AML allo-HSCT

Caira et al, Eur J Haematol 2008
ACUTE LEUKAEMIA and ASPERGILLOSIS OVER THE YEARS

6 HAEMATOLOGICAL INSTITUTIONS

INCREASING NUMBER OF AML = INCREASING NUMBER OF PATIENTS AT HIGHEST RISK

Pagano et al, Haematologica 2006
MANAGEMENT OF HIGH RISK PATIENTS

- ANTI-MOLD PROPHYLAXIS
- INTENSIVE DIAGNOSTIC WORK-UP

In 2010

Is it really necessary in all AML PATIENTS ????
A VERY SIMPLE EQUATION

HOST + ASPERGILLUS + ENTRANCE = ASPERGILLOSIS
...BUT A COMPLEX VARIABLE

- Underlying disease
- Genetic pattern
- Therapies and consequences
- Exposure
- Age and performance status

HOST
<table>
<thead>
<tr>
<th>GENETICAL FACTORS</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFECTIVE OXIDANT PRODUCTION</td>
<td>NADPH-oxidase activity within PMN aggregates prevents hyphal proliferation and tissue invasion.</td>
</tr>
<tr>
<td>SNPs IN IL-10 GENE PROMOTER</td>
<td>High IL-10 level = impaired cytokines production</td>
</tr>
<tr>
<td>TNFα RECEPTOR 2 PROMOTER</td>
<td>Low TNF-α level = impaired control of infection</td>
</tr>
<tr>
<td>SNPs IN TLR-4</td>
<td>Impaired immune signal at time of infection</td>
</tr>
<tr>
<td>POLIMORFISM IN TLR-1 e TLR-6</td>
<td>Impaired production of inflammatory cytokines</td>
</tr>
<tr>
<td>POLIMORFISM IN THE PLASMINOGEN GENE</td>
<td>Impaired immune signal at time of infection</td>
</tr>
</tbody>
</table>

Modified from Erjavec et al, Clin Microbiol Infect 2009
Exposure:

HOSPITAL-DEPENDENT

Weber et al, Med Mycol 2009
234 patients, admitted in different departments at Innsbruck Medical University (118 with HM)

A subgroup analysis showed that AML patients are more at risk for IMI when:

- smoking cigarettes ($P< 0.05$),
- living in the countryside ($P<0.05$),
- having two or more fungus exposures ($P<0.05$)
The risk of IA is not constant over all the phases of AML treatment.
Ageing and the increasing number of AML patients
“AGE” AS A KEY RISK FACTOR

CHILDREN ≠ ADULTS

• Greater ability to tolerate intensive treatments

• Less exposures
## CHILDREN vs ADULTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Cases</th>
<th>Population</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td><strong>ADULT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pagano et al, Haematologica 2006</td>
<td>1999-2003</td>
<td>213</td>
<td>3012 AML</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44</td>
<td>1173 ALL</td>
<td>3.7</td>
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<td></td>
<td></td>
<td>7</td>
<td>1979 auto-HSCT</td>
<td>0.4</td>
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<tr>
<td>Cornet et al, J Hosp Infect 2002</td>
<td>1994-1997</td>
<td>130</td>
<td>AML</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63</td>
<td>ALL</td>
<td>6.3</td>
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<tr>
<td></td>
<td></td>
<td>150</td>
<td>1175 allo-HSCT</td>
<td>12.8</td>
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<tr>
<td></td>
<td></td>
<td>24</td>
<td>2115 auto-HSCT</td>
<td>1.1</td>
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<tr>
<td><strong>PEDIATRICS</strong></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>171</td>
<td>26926 ALL</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>101</td>
<td>2219 allo-HSCT</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>822 auto-HSCT</td>
<td>0.3</td>
</tr>
</tbody>
</table>
“AGE” AS A KEY RISK FACTOR

CHILDREN ≠ ADULTS

• Greater ability to tolerate intensive treatments
• Less exposures

YOUNGER ADULTS ≠ OLDER ADULTS

• Greater ability to tolerate intensive treatments
• Less comorbidities
AML IS PRIMARILY A DISEASE OF OLDER ADULTS

- **All ages:**
  2.3/100,000

- **Age ≥ 60:**
  13.7/100,000

- **Median age:**
  65-70 years old

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AGEING OF POPULATION

AML IS PRIMARILY A DISEASE OF OLDER ADULTS

THE ABSOLUTE NUMBER OF INVASIVE ASPERGILLOSIS IN AML IS INCREASING!!!
Ageing and the increasing number of AML patients

Comorbidities and performance status
PERFORMANCE STATUS

PS at 1st diagnosis in 2,696 AL patients from the Swedish Adult Acute Leukemia Registry

Juliussøn et al, Blood 2009, 113(18)
Including sepsis, pneumonia or fungal infection.

Weiser et al, Cancer 2004

Incidence
39% vs 25%
(p 0.016)
IRON OVERLOAD

Leukaemic patients = HEAVELY TRANSFUSED

IRON OVERLOAD = *high availability of free iron*

- Fi acts as a free radical catalyser
  - MUCOSITIS

- FI has negative effect on antimicrobial functions of neutrophils, monocytes, NK and macrophages

- FI is used by fungi to promote their growth
IRON OVERLOAD IN INVASIVE ASPERGILLOSIS

Kontoyiannis et al, Cancer 2007

p-value <0.0001
Ageing and the increasing number of AML patients

Comorbidities and performance status

Changes in leukaemia treatment strategy
WHAT ARE THE MAJOR DETERMINANT FACTORS IN TREATMENT DECISIONS ???

1. PATIENT’S AGE and LIFE EXPECTANCY

2. PATIENT’S COMORBODITIES and TREATMENT TOLERANCE

3. HAEMATOLOGIST’S ATTITUDE TO INTENSIVE TREATMENT !!!

Ferrara F, The Lancet Oncology 2004
STRATEGIES IN AML OVER THE YEARS

Palliative care

HIGH DOSE cytarabine

‘60s ‘70s ‘80s ‘90s 2000 2010

3 + 7 Cytarabine + antracyclines

Auto/allo HSCT

EVEN IN OLDER PATIENTS !!!

Supportive care, side effects control
Patients 55+ reported *FIT* for intensive chemotherapy

- *1988-1991*: 42%
- **1997-2005**: 60%

p-value <0.0001

* Tailor et al, Leukemia 1995, 9(2); ** Juliusson et al, Blood 2009, 113(18)
Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe in 1998

Goldman et al, BMT1998

Patient age

The age of an individual patient remains one of the most important determinants of outcome following both allogeneic and autologous HSCT procedures. As a broad generalisation it seems reasonable to recommend limits of 65 years for autograft procedures, of 60 years for allograft procedures using HLA-identical sibling donors and of 45 years for unrelated donor transplant patients. There will always be cases

Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe

Ljungman et al, BMT2006

HSCT in children gives better results than in adults. Age cannot be seen as a single risk factor but must be taken together with other factors in the decision-making regarding HSCT. It should, however, be recognised that biological rather than chronological age is the more important determining factor for outcome. As in previous
From 1999 to 2009

+ 400% in 10 years !!
“ACUTE LEUKAEMIA” SPECIFIC EPIDEMIOLOGICAL ISSUES

- Ageing and the increasing number of AML patients
- Comorbidities and performance status
- Changes in leukemia treatment strategy
- Neutropenia and myelodisplasia
**NEUTROPENIA: A COMMON RISK FACTOR IN AML**

- **<0.5 x 10^9/l: risk of infection**
- **<0.1 x 10^9/l: high risk of IFI**

*Modified from Bodey et al, Ann intern Med 1966*
### NEUTROPENIA IN SEIFEM-2008 Study

140 Invasive Aspergillosis in patients with Acute Myeloid Leukaemia:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>57 (14/79)</td>
</tr>
<tr>
<td><strong>M/F</strong></td>
<td>1.8/1</td>
</tr>
<tr>
<td><strong>Neutropenia at onset of AI</strong></td>
<td>130 (93%)</td>
</tr>
<tr>
<td><strong>Neutropenia severity</strong></td>
<td></td>
</tr>
<tr>
<td>- Mild/moderate</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>- Severe</td>
<td>123 (95%)</td>
</tr>
<tr>
<td><strong>Mean duration of neutropenia</strong></td>
<td></td>
</tr>
<tr>
<td>- &lt;10 days</td>
<td>40 (31%)</td>
</tr>
<tr>
<td>- ≥10 days</td>
<td>90 (69%)</td>
</tr>
</tbody>
</table>

*Pagano et al, Haematologica 2009*
NEUTROPHIL IMPAIRMENTS IN AML

IT MAY RESULT FROM MULTIPLE COMPONENTS:

1. Chemotherapy
2. Bone marrow infiltration by blast cells
3. Myelodysplasia

AML with *myelodysplasia-related* changes
(WHO-2008 classification)

Vardiman et al, Blood 2009
Dysplastic vs normal PMN:
↓ fungicidal activity against yeasts
↑ susceptibility to infections in myelodysplasia

Fianchi et al, P388, 42nd Congress of the SIE, Milan 2009
“ACUTE LEUKAEMIA” SPECIFIC EPIDEMIOLOGICAL ISSUES

- Ageing and the increasing number of AML patients
- Comorbidities and performance status
- Changes in leukaemia treatment strategy
- Neutropenia and myelodysplasia

NOT ALL ACUTE LEUKAEMIA PATIENTS ARE AT THE SAME RISK !!!!
SEIFEM-2010 study:

PROSPECTIVE SURVEY ON 
PRE-HOSPITAL RISK FACTORS FOR 
INVASIVE ASPERGILLOSIS IN 
NEWLY DIAGNOSED AML

TARGET: 1000 patients in 32 ACTIVE CENTRES

Pagano et al, Clin Infect Dis 2009
HEMA e-CHART
Prospective Multicentral Registry of Febrile Events in Haematology

IN 17 CENTRES THE REGISTRY OF ALL NEWLY DIAGNOSED HAEMATOLOGICAL MALIGNANCIES

→ INCIDENCE RATES !!!

ADVANTAGES:
• PROSPECTIVE
• MULTICENTRAL
• ON-LINE
• COMPLETE INFORMATION !!!
CONCLUSIONS - I

- Invasive aspergillosis remains the most crucial infectious complication in haematological patients.

- Patients suffering from Acute Myeloid Leukaemia continue to be at the highest risk.

- In western countries the number of IA in AML is expected to increase, particularly in older patients.
In HIGH RISK categories we are moving towards a spreading of prophylaxis measures and towards an intensive diagnostic approach.

Patients with AML should be better categorized in order to target human and economic resources.

More innovative epidemiological tools are now available to search for novel factors for IA risk stratification.