Management Strategies For Invasive Mycoses:
An MD Anderson Perspective

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Antifungal prophylaxis - Minimal “standard of care”

- Autologous transplant, Acute leukemia
  - fluconazole 400 mg/day
  - *itraconazole*?

- Low-risk allogeneic
  - fluconazole 400 mg/day or

- High-risk leukemic
  - (older patients with AML/MDS, persistent neutropenia, prior history of IA)
  - voriconazole 200 mg BID or caspofungin 50 mg/day…
  - *posaconazole*?
Antifungal prophylaxis -
Minimal “standard of care”

- High-risk allogeneic
  (cord blood transplants, haploidentical, alemtuzumab recipients or prior history of fungal infection)
  - voriconazole 200 mg BID or caspofungin 50 mg/day or posaconazole? +/- aerosolized AMB-d

- aGvHD with steroids
  - voriconazole 200 mg BID or POSA 200mg TID or caspofungin 50 mg/day (inpatient)

- Liver function abnormalities
  - caspofungin 50 mg/day (inpatient) or posaconazole
Itraconazole The Past as Prologue….

Outcome of IFI

Nonfatal IFI Fatal IFI

Itraconazole Trough Concentration (ng/mL)

P = 0.039

Oral Itraconazole, Day 7 Plasma Concentrations

Itraconazole Dose/Vehicle

Voriconazole Nonlinear Pharmacokinetics

- Due to saturation of metabolism (Michaelis-Menten kinetics)
- Greater than proportional increase in exposure with increasing dose
- On average, 1.5-fold oral dose escalation from 200 mg q12h to 300 mg q12h will lead to a 2.5-fold increase in exposure
- Considerable inter-patient variability (100-fold) in PK due to CYP2C19 genotype, drug inter-actions, age, weight (≤ 40 kg)

Average Steady State Plasma Concentration, μg/mL

Voriconazole Twice Daily Dose (mg)
Voriconazole Therapeutic Drug Monitoring

- 28/188 Patients treated with voriconazole serum drug levels
  - Patient dose: 200 mg BID after loading dose
  - Indication: disease progression (17), toxicity (11)

- A significant \( P < 0.025 \) relationship between disease progression and drug concentration was described:
  - Random voriconazole concentrations > 2.05 µg/mL
    - 100% (10/10) clinical response
  - Random voriconazole concentrations < 2.05 µg/mL
    - 44% 8/18 (44%) patients with disease progression

Correlation of Posaconazole Plasma Drug Concentrations With Breakthrough IFIs?

• Efficacy: evidence of a “threshold” therapeutic concentration…
  – Effective prophylactic plasma concentration 3–5 hours after oral dose < 700 ng/mL
  – Dose response in treatment seen up to 1000–1500 ng/mL
CAS as primary prophylaxis in patients with stem cell transplant: MDACC

- Retrospective analysis, 2002-2006
- 123 patients, most with liver and/or renal dysfunction
- 117 patients with allogeneic BMT
- Median time to engraftment: 12 days
- 50 pts (41%) with GvHD and systemic corticosteroids
- Median duration of CAS prophylaxis: 73 days
- Breakthrough IFIs by day 100: 9 (7%)
  - 6 molds (2 Aspergillus, 1 Rhizopus, 1 Exserohilum, 1 unspecified)
  - 3 yeasts (Cryptococcus, C. glabrata, C tropicalis)
- Median time to IFI: 65 days, only 1 during neutropenia
- No CAS-related AEs

Chou L & Kontoyiannis DP. Pharmacotherapy. 2008
Why Did Breakthrough IFIs Occur?

- Suboptimal pharmacokinetics (e.g., low ITC, VRC, POS levels)?
- High inoculum of fungus?
- Host related (e.g., polymorphisms in innate-immunity genes)?
- Azole-resistant fungus (primary or breakthrough infection)?
- Do not forget catheters as a cause of breakthrough bloodstream IFI!
Multi-triazole (ITC, VRC, POS, RAVU)-Resistant Aspergillus

- Netherlands survey: 0/114 patients (170 A fumigatus isolates) from 1945–1998 vs. 10/81 patients (13 isolates) from 2002–2006 ($P < 0.001$)\(^1\)
- No clonality, but unique mechanism of resistant (L98H in CYP51a) in 12/13 isolates\(^1\)
- Some isolates came from patients not previously exposed to azoles\(^1\)
  - Role of OTC and agricultural use of azoles?\(^2\)

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Kontoyiannis/Lancet/2001: ref not found on PubMed. Query?
Verweij: query... still not found in Pub Med. Ck still in press?
D Balog: 26.03.2007
Empiric Antifungal Therapy in Neutropenic High-Risk Patients

• Empiric antifungal therapy is still an accepted practice in view of suboptimal early diagnosis of IFI, but this might change soon
• Empiric antifungal therapy should not substitute for careful clinical evaluation
• Antifungals should start after 3–7 days of persistent fever
• Risk stratification for the background rate of IFIs, toxicity, and cost of antifungal are important
• Several options, no clear drug of choice, decisions should be individualized
• Caspofungin, L-AmB, voriconazole (high-risk and lower-risk patients) are the most attractive
_need a reference citation for bullet 3 - there is a ref attached?
D Balog: 26.03.2007
Treatment Success for Aspergillosis: Importance of Early CT and Early Therapy


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cured, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>52.4%</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>40.9%</td>
</tr>
<tr>
<td>All Treated</td>
<td>62.3%</td>
</tr>
</tbody>
</table>

Nodular Lesion With Halo Sign (N = 143)

Nodular Lesion Without Halo Sign (N = 143)

Strategies in the Management of IFIs

- No Disease
- Cultures/Antigen
- Signs and Symptoms
- Cultures/Histopathology
- Sequelae

Prophylaxis
Pre-emptive
Empiric
Treatment
Morbidity/Mortality

Crude mortality 60% to 90%

Suggested Algorithm

Mould-active prophylaxis

Persistent neutropenic fever of unknown etiology for \( \geq 4 \) days in a patient receiving appropriate antibacterial agents

Chest CT scan

Nodule or infiltrate present

Initiate a salvage antifungal combination regimen (lipoAMB+CAS)

Positive serum GMI or \( \beta \)-glucan or recovery of *Aspergillus* from sputum or BAL

Diagnosis of probable IA established

Initiate a salvage antifungal combination regimen (lipoAMB+CAS vs CAS+VRC)

Negative findings

?Continue current antifungal vs change antifungal class (eg CAS)

Consider repeat chest CT scan after 7 days for recurrent or persistent fever of unknown etiology
Pragmatism vs. Science and Decisions to Use Combination Therapy

Scientific
- Prospective clinical trials
- Animal studies
- In vitro studies
- Mechanisms of synergy

Practical
- Spectrum of therapy
- Intensity of therapy
- Safety of therapy

Increasing net immunosuppressive state of patient
Lewis RE & Kontoyiannis DP. Br J Hematology 2005
Combination Therapy for IA
Accumulating Evidence for Benefit?


When controlled for renal failure and CMV infection, patients in the study group were 2.4 times less likely to die within 90 days compared to the control group (OR = 0.419, 95% CI, 0.14–1.3). The difference however, was not statistically significant (P= 0.12).


<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with VRC + CAS</td>
<td>0.419</td>
<td>0.139–1.263</td>
<td>0.12</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2.803</td>
<td>0.946–8.304</td>
<td>0.062</td>
</tr>
<tr>
<td>CMV infection</td>
<td>4.340</td>
<td>1.443–13.057</td>
<td>0.009</td>
</tr>
</tbody>
</table>

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Caillot et al. *Combistrat.* *Cancer* 2007

Retrospective salvage data of L-AmB + CAS in IA: ? benefit
For the lower right citations, I found no matches for Alief nor Kontoyiannis - are the references correct - year / journal?
D Balog; 26.03.2007
Echinocandins-Ideal Antifungals For Candidiasis?

**Advantages**

- Excellent in vivo *Candida* efficacy
- No cross resistance among azole-resistant *Candida* species
- Predictable pharmacokinetic profile
- Excellent safety at efficacious doses
- Low theoretical risk of drug interactions or antagonism of other antifungals

**Disadvantages**

- Notable holes in spectrum for other yeasts (e.g., *Trichosporon, Cryptococcus*)
- No oral formulation
- Not distributed in anatomically privileged sites (e.g., CNS, eye)
Echinocandin Pharmacokinetics-

Drug distribution precludes use in some forms of candidiasis

Intravenous only

Lowest  Highest

Liver & Spleen
Gut and Gall bladder
Eye
Brain/ CSF
Kidneys
Urine/ Bladder

Volume of distribution (L/kg)
Caspofungin 0.14
Micafungin 0.24
Anidulafungin 0.5
Caspofungin monotherapy treatment outcome at MDACC, 2001-2006 (n=64 patients)

Sipsas & Kontoyiannis. Submitted.
We now have some data to address this question.

**Always start with an echinocandin in candidemic patients**

- **Echinocandin**
  - Fungicidal
  - Broader spectrum
  - Improved safety

- **Azole**
  - Fungistatic
  - Oral therapy
  - Cheaper
Fungus-Specific Empiric Strategies for Progressing mycosis

Host immune suppression
• Taper steroids
• Immune augmentation
  (e.g. IFN-gamma, granulocyte transfusions)

Undiagnosed “resistant” pathogen
• switch therapy
• combination therapy
• dosage escalation

Glucose/Electrolytes Malnutrition
• Glucose control
• Iron chelation?

Surgical
• Debulking

Diagnosis?
Summary

• Empiric and pre-emptive therapy should take into account the limitation of diagnostics, local epidemiology, and spectrum of antifungals

• Every attempt for diagnosis should be made, and when cultures are available susceptibility testing should be considered

• Targeted antifungal therapy should take into account the spectrum and pharmacokinetic limitations of drugs and unique host-related issues, especially co-morbidities

Highly immunosuppressed patients with IFIs: Complex decision-making, individualized treatment plans
Thank you!