PREVENTION OF INVASIVE FUNGAL INFECTIONS IN VULNERABLE HOSTS

KIEREN A. MARR MD, MBA
PROFESSOR OF MEDICINE, JOHNS HOPKINS SCHOOL OF MEDICINE
DIRECTOR, TRANSPLANT AND ONCOLOGY INFECTIOUS DISEASES
VICE CHAIR OF MEDICINE FOR INNOVATION IN HEALTHCARE IMPLEMENTATION
COMMERCIAL ACTIVITY DISCLOSURE

• CONSULTANT / ADVISORY BOARD
  • AMPLYX, CHIMERIX, CIDARA, MERCK

• EDITORIAL ROLES
  • UPTODATE

• LICENSED TECHNOLOGY / OWNERSHIP
  • MYCOMED TECHNOLOGIES
OUTLINE

• PROPHYLAXIS – FOUNDATION AND HISTORY

• REAL-LIFE EPIDEMIOLOGY

• TRIAL DESIGN
  • RESPECT: 1-DRUG PREVENTION WITH REZAFUNGIN

• FUTURE POTENTIALS: UNMET NEEDS IN HEMATOLOGIC MALIGNANCIES
**Original Article**

**Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia**

Oliver A. Cornely, M.D., Johann Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Hoffmann, M.D., Jerzy Holowiecki, M.D., Dick Stockert, M.D., Yeow-Tee Goh, M.D., Mario Petri, M.D., Cathy Hardal, M.D., Ramachandran Suresh, Ph.D., and David Angulo-Gonzalez, M.D.*

Prepublished online Sep 8, 2010; doi:10.1182/blood-2010-02-289151

Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection (IFI) after allogeneic hematopoietic cell transplantation (HCT)

AZOLE PROPHYLAXIS - BMT

• FLUCONAZOLE PREVENTS CANDIDIASIS
  • NEW COMPARATOR FOR MOLD-ACTIVE AZOLES

• TWO RANDOMIZED TRIALS EVALUATING ITROCONAZOLE SOLUTION IN BMT PATIENTS
  • BOTH
    • DECREASED INVASIVE ASPERGILLOSIS IN ITROCONAZOLE ARM
    • TREND TO WORSE SURVIVAL IN ITROCONAZOLE ARM

• TOXICITIES OF DRUG
  • GI TRACT TOXICITIES
  • DRUG INTERACTIONS

Is decreased IA “caused” by informative censoring?

Marr et al, Blood 2004 103(4): 1527-33
POSACONAZOLE

- POSACONAZOLE VS. FLUCONAZOLE (N=600 PATIENTS)
  - DRUG WITH DIAGNOSIS OF GVHD
- APPROVED FOR PROPHYLAXIS IN BMT & AML/MDS

Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation


600 PATIENTS ENROLLED IN NHLBI BMT CTN PROTOCOL 0101

Mould-active prophylaxis: voriconazole

Standard risk allo HCT

1° endpoint: fungal free survival

Day 120-180

Fluconazole + targeted therapy (GM EIA)
# ANTIFUNGAL PROPHYLAXIS TRIALS IN BMT PATIENTS

## Ullmann trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>POS n (%)</th>
<th>FLU n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Period (120 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16 (5)</td>
<td>27 (9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>7 (2)</td>
<td>21 (7)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

N=600 total patients (301 POS group, 299 FLU group).

## BMT CTN trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>VORI n (%)</th>
<th>FLU n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Period (180 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14 (4.6)</td>
<td>24 (8.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>9 (3.0)</td>
<td>17 (5.8)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

N=600 total patients (305 VORI group, 295 FLU group).

Risk reduction 0.037 vs. 0.04
ISAVUCONAZOLE

• APPROVED FOR THERAPY OF INVASIVE ASPERGILLOSIS
• OBSERVATIONS: USED FREQUENTLY, ESPECIALLY WITH LIVER TOXICITIES, PEOPLE WITH LONG QT
• REPORTS OF FREQUENT BREAKTHROUGH
• REASONS UNKNOWN
  • BIAS?
  • ANTIFUNGAL LEVELS? (TDM)
  • RESISTANCE? AT LEAST ONE CASE OF TR34-L98H RESISTANT A. FUMIGATUS BREAKTHROUGH REPORTED

REAL-WORLD EPIDEMIOLOGY

- CIBMTR STUDY – ACUTE LEUKEMIA WITH ALTERNATIVE DONORS: MATCHED, UNRELATED DONORS (MUD), MISMATCHED, UNRELATED DONORS (MMUD) AND CORD BLOOD (UCB)

- INCIDENCE OF IFI REMAINS HIGH

- “PREVENTABLE IFI”:
  - BOTH IA AND CANDIDIASIS

Ballen et al. BBMT 2016 22(9)
REAL – WORLD RECURRENT INFECTIONS

- INFECTIOUS MORBIDITY BETTER APPRECIATED AS CUMULATIVE, RECURRENT EVENTS
- SWIMMER-LANE PLOTS: PROVIDE CONTROL FOR INFORMATIVE CENSORING AND DEMONSTRATES ‘REAL-LIFE’ FAILURE
- A LOT OF MORBIDITY DESPITE EFFECTIVE PREVENTION ALGORITHMS
- HETEROGENEITY
- IFI OCCUR LARGELY BEFORE DEATH
SUCCESS = BALANCE

Benefits
- Prevent IFI
- morbidity
- mortality
- Secondary

Risks
- Toxicities
- Drug interactions
- Drug resistance
- Costs

Each drug has different benefits and risks when utilized in different settings.
PNEUMOCYSTIS INFECTION
FRENCH BMT OBSERVATION

• ONLY 45% OF 139 CONSECUTIVE PATIENTS RECEIVED FULL COURSE OF TMP/SMX
  • 60 PATIENTS SWITCHED DUE TO SIDE EFFECT
  • 18 CONFIRMED PCP CASES (12.9% INCIDENCE)
• FREQUENT FAILURE DUE TO POOR TOLERABILITY IN REAL-WORLD

Fig. 1 Flow chart of pneumocystis prophylaxis in 139 consecutive allogeneic HCT recipients

Redjoul et al. BMT 2019 54: 1082-88
REZAFUNGIN

ANTIFUNGAL PROPHYLAXIS: RATIONALE

- ONCE – WEEKLY INFUSION
- NO CYTOCHROME P450 INTERACTIONS
- PRECLINICAL, CLINICAL ACTIVITY AGAINST CANDIDA SPP.
- PRECLINICAL ACTIVITY AGAINST ASPERGILLUS & PCP
Rezafungin
Aspergillosis & PCP models

Aspergillosis in neutropenic mice:
Equivalent survival in humanized doses relative to AmB

PCP in neutropenic and steroid-suppressed mice:
Equivalent reduction in cysts and trophic forms relative to TMP/SMX

10 mg/kg ≈ human dose of 200mg
20 mg/kg ≈ human dose of 400mg

Cushion et al. TCT, Feb 2019
RESPECT TRIAL
ANTIFUNGAL PROPHYLAXIS
IN BMT

• TO START Q1 2020 IN EUROPE

• RANDOMIZED, DOUBLE-BLIND COMPARISON OF ONCE WEEKLY REZAFUNGIN VS. STANDARD ANTIFUNGAL PROPHYLAXIS (AZOLE + TMP-SMX) AFTER ALLOBMT

• DESIGN (462, 2:1 RANDOMIZATION)
  • STANDARD-RISK ALLOGENEIC BMT (NO CBT, AML NOT IN MORPHOLOGIC REMISSION, RECENT IFI)
  • 90 DAYS REZA VS. CURRENT STANDARD (FLUCONAZOLE WITH POSA FOR GVHD & TMP/SMX)
  • POWERED TO MEASURE NON-INFERIORITY OF FUNGAL – FREE SURVIVAL & SUPERIORITY OF PROPHYLAXIS SUCCESS
RESPECT PHASE 3 TRIAL

1° Endpoint: Fungal Free Survival at Day 90

Rezafungin Arm (n=~300)

Week 1 2 3 4 5 12 13
Rezafungin
Azole placebo
Bactrim placebo

Day 1

Comparator Arm (n=~150)

Week 1 2 3 4 5 12 13
Rezafungin Placebo
Azole*
Bactrim

Day 1

Follow up

*Fluconazole to start in all patients. Posaconazole optional in patients who develop GVHD per label.
FUTURE APPLICATIONS?
UNMET NEEDS IN HEMATOLOGY

• INFECTIOUS RISKS POORLY DESCRIBED IN CLINICAL DEVELOPMENT

• EXPERIENCE UNDERLINING COMPLEX SECONDARY RISKS FOR IFI IN SEVERAL DRUGS

• MANY CONTRAINdications TO AZOLES DUE TO CYTOCHROME P450 INTERACTIONS

**New chemotherapeutic agents already in use or coming in Hematology**

<table>
<thead>
<tr>
<th>AML</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FLT3-inhibitors (Quizartinib, Midostaurin, Sorafenib)</td>
<td>1. Monoclonal antibodies</td>
</tr>
<tr>
<td>2. Monoclonal antibodies anti-CD33 (Gentuzumab)</td>
<td>a. anti-CD19 (Blinatumumab)</td>
</tr>
<tr>
<td>3. Arsenic Trioxide</td>
<td>b. anti-CD22 (Inotuzumab)</td>
</tr>
<tr>
<td>4. IDH1-2 inhibitors</td>
<td>2. TK inhibitors (Imatinib, Nilotinib, Dasatinib, Ponatinib)</td>
</tr>
<tr>
<td>5. Combined liposomal cytarabine and daublastine (CTX1)</td>
<td></td>
</tr>
</tbody>
</table>

**Lymphomas (low and high grade)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BTK-inhibitors (Ibrutinib)</td>
<td>1. IMiDS (Talidomide, Lenalidomide Pomalidomide)</td>
</tr>
<tr>
<td>2. Monoclonal antibodies anti-CD20 (Rituximab, Ofatumumab)</td>
<td>2. Proteosome inhibitors (Bortezomib, Carfizomib)</td>
</tr>
<tr>
<td>3. PI3Kδ signaling- inhibitor (Idelalisib)</td>
<td>3. Monoclonal antibodies</td>
</tr>
<tr>
<td></td>
<td>a. anti-CD38 (Daratumumab)</td>
</tr>
<tr>
<td></td>
<td>b. anti-CD319 (Elotuzumab)</td>
</tr>
</tbody>
</table>

**Hodgkin’s Lymphoma**

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Monoclonal antibodies anti-CD30 (Brentuximab)</td>
</tr>
<tr>
<td>2. IgG4 anti-PD-1 (Nivolumab)</td>
</tr>
</tbody>
</table>

**Multiple Myeloma**

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IMiDS (Talidomide, Lenalidomide Pomalidomide)</td>
</tr>
<tr>
<td>2. Proteosome inhibitors (Bortezomib, Carfizomib)</td>
</tr>
<tr>
<td>3. Monoclonal antibodies</td>
</tr>
<tr>
<td>a. anti-CD38 (Daratumumab)</td>
</tr>
<tr>
<td>b. anti-CD319 (Elotuzumab)</td>
</tr>
</tbody>
</table>

**CLL**

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BTK-inhibitors (Ibrutinib)</td>
</tr>
<tr>
<td>2. Monoclonal antibodies anti-CD20 (Ofatumumab)</td>
</tr>
<tr>
<td>3. PI3Kδ signaling- inhibitor (Idelalisib)</td>
</tr>
<tr>
<td>4. Anti apoptotic BCL-2 (Venetoclax)</td>
</tr>
</tbody>
</table>
IFI RISKS ARE COMPLEX AND SOMETIMES UNEXPECTED

- RISKS REPRESENT
  - CUMULATIVE FUNCTION OF HOST RISKS (EX. AGE, LUNG DISEASE), UNDERLYING DISEASE, PRIOR THERAPIES
  - MANY DRUGS (EX. CHECKPOINT INHIBITORS) CAUSE INFLAMMATORY SYNDROMES THAT REQUIRE SECONDARY IMMUNOSUPPRESSION
    - EXAMPLE: IFI AFTER STEROIDS GIVEN FOR PNEUMONITIS, COLITIS
  - NON-SPECIFIC EFFECTS OF ‘TARGETED’ DRUGS
TYROSINE KINASE INHIBITORS

- DRUGS TARGET B CELL RECEPTOR, INHIBIT ACTIVATION AT DIFFERENT SIGNALING TARGETS. USED FOR CLL, LYMPHOMAS

- IFI RISKS COMPLICATED. EXAMPLE IBRUTINIB (BRUTON’S TK INHIBITOR)
  - SINGLE-CENTER REVIEW: 11% INCIDENCE INFECTION
  - RELATIVELY HIGH INCIDENCE IFI (ESPECIALLY PCP & IA)
  - CNS ASPERGILLOSIS
  - MECHANISTIC STUDIES REVEAL INHIBITION OF MACROPHAGE AND PMN KILLING

- LIMITED OPTIONS FOR PROPHYLAXIS DRIVING EXPLORATION OF ALTERNATIVES

CONCLUSIONS

• LONG HISTORY OF STUDIES IN BMT DEMONSTRATE UTILITY OF ANTI-FUNGAL PROPHYLAXIS IN TRIALS
  • ANTI-CANDIDA, ASPERGILLUS AND PJP
• REAL-LIFE OUTCOMES COMPLICATED BY INABILITY TO TAKE PREVENTATIVE DRUGS FOR A LONG PERIOD OF TIME (DRUG INTERACTIONS, TOXICITIES)
• NEW STUDY TO START NEXT YEAR:
  • REZAFUNGIN 1-DRUG PROPHYLAXIS VS. STANDARD APPROACH
  • DESIGN CONSIDERS LESSONS LEARNED
• EVOLVING COMPLEX FIELD WITH UNMET NEEDS IN OTHER VULNERABLE HOSTS, ESPECIALLY WITH TARGETED BIOLOGICS
THANK YOU