HOW TO DEFINE RESPONSE IN ANTIFUNGAL CLINICAL TRIALS?
MORTALITY ASSOCIATED WITH INVASIVE ASPERGILLOSIS


Mortality over time (days):
- n = 178
ASPERGILLOSIS: A SEVERE DISEASE IN SEVERELY ILL PATIENTS

223 cases over 8 years

Survival (%)

Time (months)

13%

Courtesy Raoul Herbrecht
VORICONAZOLE VERSUS AMFOTERICIN B IN INVASIVE ASPERGILLOSIS: SURVIVAL


![Graph showing survival rates for Voriconazole and Amphotericin B in invasive aspergillosis.](image-url)
HIGH VERSUS STANDARD DOSE AMBISOME FOR INVASIVE MOULD INFECTIONS

AmBisome 10 mg/kg x 14 followed by 3 mg/kg/day

201
proven & probable
Invasive mould infections

End of treatment Favorable response

Survivors

94
46%

107
50%

59%

72%
THE CLINICAL TRIAL AS GUIDANCE FOR DAILY PRACTICE
### Difficulties in the Assessment of Treatment of Invasive Fungal Disease

<table>
<thead>
<tr>
<th>Clinical practice</th>
<th>Clinical trials</th>
<th>Statistics</th>
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</thead>
</table>

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DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical practice

WEAK SPOTS

Clinical trials

Statistics
DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

WEAK SPOTS

- Clinical practice
- Clinical trials
- Statistics

TRIAL POPULATION

CRITERIA FOR ASSESSMENT

STUDY DESIGN
DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical practice

Clinical trials

Statistics

WEAK SPOTS

CLINICIAN

STATISTICIAN

TRIAL POPULATION

CRITERIA FOR ASSESSMENT

STUDY DESIGN
DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical practice

Statistics

CLINICIAN

STATISTICIAN
CHANGING ROLE OF THE STATISTICIAN

CLINICIAN

Can I be of any help??

STATISTICIAN
No!!! You got it wrong! It is not ‘superior’ or ‘inferior’ It is “Not non-inferior”
CONFLICT OF SCIENCE AND CLINICAL CARE

statistician

expert

clinician

trial data
DIFFICULTIES IN THE ASSESSMENT OF TREATMENT OF INVASIVE FUNGAL DISEASE

Clinical trials

WEAK SPOTS

TRIAL POPULATION

CRITERIA FOR ASSESSMENT

STUDY DESIGN
PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

CRITERIA FOR OUTCOME

STUDY DESIGN
PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

IN-/EXCLUSION CRITERIA

DEFINITION OF DISEASE

CRITERIA FOR OUTCOME

STUDY DESIGN
PREREQUISITES TO INTERPRET CLINICAL TRIAL DATA

TRIAL POPULATION

IN- /EXCLUSION CRITERIA

DEFINITION OF DISEASE

CRITERIA FOR OUTCOME

STUDY DESIGN
POTENTIAL IMPACT IN/EXCLUSION CRITERIA ON A TRIAL POPULATION
DIAGNOSIS OF A FUNGUS

Invasive fungus

4% in trials !!

REPRESENTATIVE ?!
PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

IN- /EXCLUSION CRITERIA

DEFINITION OF DISEASE

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CRITERIA FOR OUTCOME

STUDY DESIGN
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TRIAL POPULATION

CRITERIA FOR OUTCOME  STUDY DESIGN
SUCCESS - FAILURE

PATIENT
keep alive

DOCTOR

DISEASE
efficacy

THERAPY
JUDGEMENT OF INTERVENTION

STRATEGIC TRIAL --------- versus --------- DRUG TRIAL

PATIENT

keep alive

DOCTOR

DISEASE

efficacy

THERAPY
PARAMETERS FOR JUDGEMENT

STRATEGIC TRIAL --------- *versus* --------- DRUG TRIAL

- survival
- costs
- quality of life

- regression
- toxicity,
  tolerance
JUDGEMENT OF INTERVENTION

STRATEGIC TRIAL \textit{versus} DRUG TRIAL

disease

efficacy

therapy
RESPONSE CLINICAL TRIALS

• SUCCESSFUL
  ✓ Complete response
  ✓ Partial response

• FAILURE
  ✓ Stable
  ✓ Progression
  ✓ Death

• NON-EVALUABLE
  ✓ Indeterminate
  (conflicting data)
RESPONSE CLINICAL TRIALS

- **SUCCESSFUL**
  - Complete response
  - Partial response
  - Stable

- **FAILURE**
  - Progression
  - Death

- **NON-EVALUABLE**
  - Indeterminate (conflicting data)
TRIAL PARAMETERS FOR SUCCESS

*defervescence
*normalization related signs & symptoms
*fungus-related mortality (autopsy)
*eradication/prevention of organism
  (few positive cultures - surrogates)
*completion of therapy course
*overall survival
  (at EOT, day 10, 30, 60, 90, 120??)
JUDGEMENT OF INTERVENTION

STRATEGIC TRIAL --------- *versus* --------- DRUG TRIAL

- **PATIENT**
  - *keep alive*
- **DOCTOR**
TRIAL PARAMETERS FOR SUCCESS

*defervescence*

*normalization related signs & symptoms*

*fungus-related mortality*

*eradication/prevention of organism*

*completion of therapy course*

*overall survival*

(at EOT, day 10, 30, 60, 90, 120??)
CLINICIAN’S APPRECIATION OF SUCCESS

*defervescence*

*normalization related signs & symptoms*

*survival*
CLINICIAN’S APPRECIATION OF SUCCESS

*defervescence
*MORBIDITY
*fungus-related mortality
*eradication/prevention of organism
*completion of therapy course
*MORTALITY
(at EOT, day 10, 30, 60, 90, 120??)
PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

CRITERIA FOR OUTCOME

STUDY DESIGN
PREREQUISITES TO INTERPRETE CLINICAL TRIAL DATA

TRIAL POPULATION

CRITERIA FOR OUTCOME

STUDY DESIGN
MAIN MOTIVATION FOR TRIALS

effectiveness / safety of a strategy

ORGANISMS -- CLINICAL SYNDROMES

effectiveness / safety of a new drug (vs established one)

industry

community
STRATEGIC TRIAL as a DRUG-EFFICACY TRIAL
POSACONAZOLE vs AZOLES AS PROPHYLAXIS IN MYELOID MALIGNNCIES

Randomized; AML, MDS 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>AZOLES</th>
<th>POSACONAZOLE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>400 mg/day iv/po</td>
<td>200 mg/day tid</td>
</tr>
<tr>
<td>n = 298</td>
<td></td>
<td>n = 304</td>
</tr>
<tr>
<td>INVASIVE FUNGUS</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>ASPERGILLOSIS</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>FATAL FUNGUS</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>OVERALL MORTALITY</td>
<td>22%</td>
<td>16%</td>
</tr>
<tr>
<td>SERIOUS ADVERSE EVENTS</td>
<td>2%</td>
<td>6%</td>
</tr>
</tbody>
</table>
PUTATIVE ANTIFUNGAL STRATEGY

PROPHYLAXIS    EMPIRICAL  (PRE-EMPTIVE) THERAPY

P  E  T

DIAGNOSTICS

ULLMANN – CORNELY REPORTS

P  E  T

DIAGNOSTICS

End of treatment episode

- Aspergillosis
- Fungal death
- Overall mortality
Death as a parameter of outcome

Death and survival depend on:
- Treatment underlying disease
- Treatment of complications including infections

Survival of infections depends on:
- Early diagnosis
- Timely intervention
- Selection of adequate anti-infectives

Death and survival are 'endpoints' of a complete strategy during the risk episode.
POSACONAZOLE ASPERGILLOSIS PROPHYLAXIS STUDIES (2)

ULLMANN – CORNELY STUDIES

POSA

?E?

?T?

?DIAGNOSTICS?

End of treatment
- Aspergillosis
- Fungal death
- Overall mortality

FLU

?E?

?T?

?DIAGNOSTICS?

End of treatment
- Aspergillosis
- Fungal death
- Overall mortality
POSACONAZOLE ASPERGILLOSIS PROPHYLAXIS STUDIES (4)

ULLMANN – CORNELY AS STRATEGIC STUDIES

**START**

- **POSA**
  - Protocol dictated start of treatment
  - Fixed diagnostics

- **NO DRUG**
  - Start treatment at perceived need
  - Fixed diagnostics

**END OF TREATMENT**

- Aspergillosis
- Fungal death
- Overall mortality
Use of empirical and prophylactic trials to assess drug efficacy
PROPHYLAXIS

- POSA CONAZOLE

EMPIRICAL

- CASPO FUNGIN - LIPOSOMAL AMPHO B

THERAPY

- VORICONAZOLE
The best choice is always the most effective agent against a given pathogen

-independent of strategy
  (prophylaxis, empirical, etc)

-selection may be influenced by inconveniences
  (formulation, tolerance, interactions, price)
POSACONAZOLE RESULTS
FIRST LINE TREATMENT ASPERGILLOSIS
SALVAGE FOR INVASIVE ASPERGILLOSIS

**Refractory / intolerant amphotericin B**

- Posaconazole: n=107, response 40%
- Amphotericin B lipid complex: n=107, response 40%
- Caspofungin: n=146, response 40%
- 'Totocidafun': n=xxx, response 40%
KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

• entry criteria

• course of underlying disease

• concurrent medication

• carry-over effect previous antifungals
KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

• entry criteria

• course of underlying disease

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WEAK SPOTS OF SALVAGE TRIALS IN INVASIVE FUNGAL DISEASE

“REFRACTORY TO OR INTOLERANT OF…”

MIXED POPULATION WITH:

- Subjective entry criteria
- Less sick patients with oral compounds
- Carry-over effect of previous antifungals
CASES FOR RESCUE?

INTOLERANT:
OBJECTIVELY VERIFIABLE ORGAN TOXICITY

SUBJECTIVE INTOLERABILITY

REFRACTORY:
NO RESPONSE, STABLE PROGRESSION
INTOLERANT: OBJECTIVELY VERIFIABLE ORGAN TOXICITY

OBJECTIVELY VERIFIABLE ORGAN DYSFUNCTION
- Drug-related fever, exanthema
- Organ dysfunction

SUBJECTIVE INTOLERABILITY
- Nausea, vomiting, chills, malaise (>5 days)

REFRACTORY:
- No response, stable progression
- Low granulocyte count
- Increasing granulocyte count
- Intolerance to toxicity
- A single shiver
- Hyperpyrexia
- Creatinine increase
- Renal failure
- Potassium levels increase
- Renal failure

FAILURES?
CASES FOR RESCUE?

INTOLERANT:
OBJECTIVELY VERIFIABLE ORGAN TOXICITY

SUBJECTIVE INTOLERABILITY

REFRACTORY:
NO RESPONSE, STABLE PROGRESSION
INTOLERANT: OBJECTIVELY VERIFIABLE ORGAN TOXICITY

SUBJECTIVE INTOLERABILITY

REFRACTORY: NO RESPONSE, STABLE PROGRESSION
EVOLUTION OF CT-LESIONS DUE TO PULMONARY ASPERGILLOSIS

Number of lesions

Size of lesions in cm³

0 2 4 6 8 10 12 14

0 7 14 21 28 35 42 49 56 63

days
LUNG LESIONS vs GALACTOMANNAN AS PARAMETERS FOR INVASIVE ASPERGILLOSIS


19 patients recovering from neutropenia

no change antifungals

19 galactomannan normalization

16 recovery

3 unrelated death
COURSE OF β-D-GLUCAN TO MONITOR THERAPY OF INVASIVE FUNGAL INFECTIONS

95 patients treated for acute leukemia

190 neutropenic episodes

β-D-glucan pg/ml

Response
No response

Time after onset of fever
KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

• entry criteria

• course of underlying disease

• concurrent medication

• carry-over effect previous antifungals
MULTIVARIATE ANALYSIS
PROGNOSIS FACTORS IN 223 PATIENTS

Non-progressive cancer: 58%
Progressive cancer: 19%

Courtesy Raoul Herbrecht
CONSIDERATIONS ON THE EXPLORATION OF COMBINATION THERAPY

neutrophils // cellular immunity
CONSIDERATIONS ON THE EVALUATION OF A GIVEN DRUG

Graph showing response over time from diagnosis to 3 months for drugs A and B with neutrophils and cellular immunity indicated.
CONSIDERATIONS ON THE EVALUATION OF A GIVEN DRUG

diagnosis  //  3 months

response

neutrophils  //  cellular immunity

drug a
CORDYCEPS UNITARIUS

©L. Gilbert UT Austin
MORE MONEY THAN SENSE?

- neutrophils // cellular immunity
- drug a
- drug b
- drug c

3 months
KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

- entry criteria
- course of underlying disease
- concurrent medication
- carry-over effect previous antifungals
CORTICOSTEROIDS AND SURVIVAL OF ASPERGILLOSIS IN HSCT


51 patients with aspergillosis
41 allo HSCT
10 auto

Low dose corticosteroids

High dose

Graph showing survival rates over weeks with low dose and high dose corticosteroids.
KEY POINTS IN THE ASSESSMENT OF RESCUE STUDIES

• entry criteria

• course of underlying disease

• concurrent medication

• carry-over effect previous antifungals
THE TRUE MERITS OF A SALVAGE THERAPY

DRUG A

DRUG B

[Diagram showing comparison between Drug A and Drug B]
A salvage study is, as per definition, a strategy study and **NOT** suited for assessment of drug efficacy.
FATE OF MANY A CLINICAL TRIAL
LIFE IS FULL OF DIFFICULT CHOICES

“Paper or plastic?”