TREATMENT OUTCOMES OF AIDS ASSOCIATED CRYPTOCOCCAL MENINGITIS AT MTRH, ELDORET

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INTRODUCTION

- Cryptococcosis: invasive fungal infection caused by *Cryptococcus neoformans*<sup>1,2</sup>.
- Predisposing factor: profound CMI defect<sup>3</sup>.

Cryptococcal meningoencephalitis: most frequent manifestation of cryptococcosis in HIV-infected patients<sup>4</sup>.

- Occur when CD4<sup>+</sup> count < 100 cells/µl (1<sup>st</sup> manifestation in up to 1/3)
- Reduces life of AIDS patients by 2yrs regardless of the CD4 count<sup>6</sup>

- High mortality in the 1st 2 wks
BACKGROUND

- Pre AIDS era: rare: < 300 /yr in USA⁶

- AIDS era: pre-cART
  - Annual incidence of 6 to 10% in USA & Europe⁷
    - 77 to 89% of meningitis in AIDS pts in N/York

- Sub-Saharan Africa; 25-30% (hospital based, lab or PM)
  - KNH: 5.2% (based on Indian ink)¹⁴
  - KNH: 5.3% (PM)¹²
  - MTRH: 12% (Reason for admission- 2006)
PROBLEM STATEMENT

- Crypto. Meningitis affects 30% of AIDS pts in SSA.
- Contributes 11-44% of deaths (Pfaller et al)
- Limited resources; 1\textsuperscript{st} line drugs unavailable, erratic supply of Amphotericin B.
PROBLEM STATEMENT QUESTIONS

- What are the clinical and mycological outcomes of AIDS associated cryptococcus meningitis at MTRH?

- Is there a difference in these outcomes when using amphotericin B or fluconazole?
OBJECTIVES

- Broad objectives

  1. To determine treatment outcomes of AACM at MTRH

  2. To determine difference in outcomes using amphotericin B or fluconazole during induction
OBJECTIVES

Specific objectives

1. To determine clinical and mycological outcomes of AACM at MTRH on day fourteen

2. To determine the difference in outcomes using amphotericin B and fluconazole
STUDY JUSTIFICATION

- High acute mortality rate

- Varying data on outcomes using fluconazole or Amphotericin B alone during induction.

- No local data evaluating treatment outcome
LITERATURE REVIEW

Clinical outcomes

- Untreated, 100% clinical/mycological failure, with acute mortality rate (AMR) of 80% (Ford et al)

- With optimal treatment; AMR of 15% (range 5 – 30%)

- Induction with single agents has varied outcomes too.
LITERATURE REVIEW- COMBINATIONS

- Amphot.B (0.7mg/kg) + 5FC vs. amphot.B alone
  - Clinical & mycological success of 60% vs. 51% (p=0.06.)
  - Overall acute MR of 5.5% (Van der Horst, 1997)

- Amapho.B vs. Amapho.B + 5FC vs. Amapho.B +FLC 400mg/d or all the three drugs combined
  - Cryptococcus clearance rate faster with Amphi.B/5 FC combination (Brouwer et al, 2004)
LITERATURE REVIEW - COMBINATIONS

- Mycological success: (Moottsikapun et al, 2004)
  
  - Ampho.B/5FC : 84%,
  
  - Ampho.B/ITC : 92%
  
  - Ampho.B/FLC (400mg): 87% respectively
COMBINATION AGENTS

- Fluconazole (Milefchik, 1997)
  - 800mg: 75%
  - 1200mg: 87%
  - 1600mg: 69%
  - 2000mg + 5FC: 82%
LITERATURE REVIEW- MONOTHERAPY

Monotherapy: FLC 800mg/day to 11 pts
  - 54.5% mycologic cure
  - Acute MR of 18.2% (Menichetti)

Fluconazole 800mg, 1200, 1600mg or 2000mg alone
  - clinical/mycological cure rates of 11%, 37%, 62% & 62% respectively (Milefchik, 1997)

Fluconazole 600mg in 19 pts: 100% mycological cure (Moottsikapun, 2003)
RECOMMENDED TREATMENT:
HIVMA/IDSA, 2008

- Induction: 1st 2 weeks
  1- Ampho.B (0.7mg/kg) + 5FC (A1)
  2- Ampho.B + FLC 400mg (BII)
  3- Ampho.B alone (BII)
  4- FLC 400mg to 800mg + 5 FC (CII)
METHODOLOGY

- Study design
  - cohort study
STUDY AREA

- MTRH, in Eldoret, serves a population of ~ 13 millions
- Inpatients in the medical wards 1 & 2
**STUDY POPULATION**

- HIV-infected pts presenting with neurological signs & symptoms.

- Case definition: laboratory: either +ve Indian ink, csf culture or CRAG.

- Consecutive sampling of cases

- Choice of antifungal: availability, ampho.B preferred to FLC.

- Study period: June 2007 to February 2008
Inclusion criteria

- Admitted in the medical wards at MTRH
- Positive test for HIV-1 antibody
- First episode of AIDS associated cryptococcus meningitis based on either positive Indian ink, CSF culture or positive CRAG.
- Age ≥13 yrs
EXCLUSION CRITERIA

1. Patients on treatment for tuberculosis

2. Patients / Parents / guardian declined to participate

3. Receiving both drugs during the 1st 14 days
Successful treatment of AIDS associated cryptococcus meningitis (survival & mycological) at two weeks varies

- using amphotericin (0.7 -1 mg/d) alone is estimated at ~ 68% (range 38% to 100%)

- and ~ 47% (range 11% to 87%) for high dose fluconazole (400mg to 800mg)

**Sample size**

- Sample size \( n \) = \[ p_1 (1 - p_1) + p_2 (1 - p_2) \] \( \times \) \( C_{p, \text{power}} \) \( (p_1 - p_2) \)

- Where \( n \) is the sample size
  - \( P_1 \) is the response rate of amphotericin B (~ 68%)
  - \( P_2 \) is the response rate of fluconazole (~ 47%)
  - \( C_{p, \text{power}} \) is a constant defined by the level of statistical significance (0.05) and Power (80%) values chosen in this study; it equates to 7.9.
Therefore;

\[(n) = \left[0.68(1 - 0.68) + 0.47(1 - 0.47)\right] / (0.68 - 0.47)^2 \times 7.9\]

\[= 0.2176 + 0.2491 / (0.21)^2 \times 7.9\]

\[= 0.4667 / 0.0441 \times 7.9 = \sim 10.583 \times 7.9 = \sim 84 \text{ patients}\]

Thus, each treatment arm should have \sim 42 patients each.
DATA COLLECTION METHODS

- A data collection tool administered
- Captured demographic data / contacts / parents / guardian / drug history
- History & clinical exam: special emphasis on the central nervous system: signs of meningism
- Laboratory data: CSF fungal studies; day 1 & 14 (only if culture positive on day 1)
- Side effects of treatment drugs
FLOW OF PATIENTS

- All patients with neurologic signs/sy admitted to the medical wards by admitting medical team

- LP done after fundoscopy by researcher. Sample taken to the laboratory immediately

- HIV positive patients meeting case definition of cryptococcus meningitis started on treatment by admitting physician

- Cases consecutively recruited by the researcher after consenting, within 24 hrs.

- Followed daily for fourteen days. Researcher repeated LP on day fourteen, for fungal cultures if initially positive.
MANEUVERS

- Consent signing

- Lumbar puncture: CSF

  (a) 3mls: microbiological examination: Gram stain, Ziehl-Neelsen (ZN) stain and India ink stain

  (b) 2mls: biochemical tests: protein & sugar estimation

  (c) 4mls: Cultures: blood agar and chocolate agar (in presence of 5-10% CO2), Sabouraud agar (without antibiotics) & MIGIT .

  (d) 2mls for CRAG

- Done at admission and day fourteen (for culture +ve only)
Culture on blood agar were incubated at 37°C and sabouraud agar was incubated at room temperature.

Observed for a period of 3 weeks.

Adequate humidity within the incubator (Petri dish with water within.)

Culture for acid fast bacillus (AFB): MIGIT: 3WKS.
DATA ENTRY AND ANALYSIS

- The data was entered into the computer by the researcher.

- Double data entry for quality control using EpiData v2.1.

- A biostatistician consulted to assist in data analysis.


- A p-value of < 0.05 was considered significant in all analyses.
Descriptive statistics (frequency listing) used to analyze categorical variables (sex, negative / positive, normal / altered mental status)

Mean, median, range & standard deviation used to analyze continuous variables: (age, temp, CSF glucose / protein)

Chi square test used to assess association between categorical variables & predictor variables:

T-test used to compare means of continuous variables

Fisher’s exact test used in a 2x2 contingency table when cell counts < 10.
Odds ratio to assess characteristics that are associated with negative CSF at 2 weeks. Analyzed at 95% CL

Multivariate logistic-regression model was used to assess association between binary outcomes (mycologic failure/success) and a set of variables during therapy.
ETHICAL CONSIDERATION

- IREC approval
- Consent signing
- Next best available treatment given
- Other recommended practices.
- No risk in participating
FIGURE 1: SCREENING AND ENROLLMENT OF PARTICIPANTS IN TREATMENT OUTCOMES OF AIDS ASSOCIATED CRYPTOCOCCUS MENINGITIS STUDY AT MTRH, ELDORET.

273 HIV-infected patients with signs and symptoms of meningitis

5 patients with 2nd episode of cryptococcal meningitis excluded

91 patients with 1st episode cryptococcal meningitis included

177 patients with negative CSF studies for cryptococcal meningitis excluded

42 patients initiated on Amphotericin B 50mg daily for 14 days

49 patients initiated on fluconazole 800mg daily for 14 days
### Table 1: Summary of Baseline Characteristics of 91 Patients with AIDS Associated Cryptococcus Meningitis Treated with Amphotericin B and Fluconazole

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Amphotericin B (42)</th>
<th>Fluconazole (49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs): Median (Range)</td>
<td>38 (28 – 65)</td>
<td>34 (20 – 67)</td>
<td>0.5775</td>
</tr>
<tr>
<td>Males; no. (%)</td>
<td>23 (54%)</td>
<td>27 (55%)</td>
<td>0.1850</td>
</tr>
<tr>
<td>Weight: mean: range (kg)</td>
<td>45.3 (39 – 82)</td>
<td>51.2 (41 – 78)</td>
<td></td>
</tr>
<tr>
<td>Known HIV status, presenting with CM for the first time.</td>
<td>16 (39%)</td>
<td>17 (35%)</td>
<td>0.2656</td>
</tr>
<tr>
<td>Patients on ARVs</td>
<td>12 (28.5%)</td>
<td>11 (22%)</td>
<td>0.2483</td>
</tr>
<tr>
<td>CD4+ count (cells/mm³) *1: Median (Range)</td>
<td>55 (0 – 256)</td>
<td>83 (0 – 188)</td>
<td>0.1783</td>
</tr>
<tr>
<td>CSF Indian ink positive: number (%)</td>
<td>14 (33%)</td>
<td>19 (38%)</td>
<td>0.6966</td>
</tr>
<tr>
<td>CSF Culture positive for cryptococcus: no (%)</td>
<td>17 (40.5%)</td>
<td>14 (28.6%)</td>
<td>0.3922</td>
</tr>
<tr>
<td>CSF CRAG positive: number (%)</td>
<td>42 (100%)</td>
<td>49 (100%)</td>
<td></td>
</tr>
<tr>
<td>CSF Glucose: mean (range) in mmol/L</td>
<td>2.18 (0.3 - 3.2)</td>
<td>2.4 (0.4 - 5.3)</td>
<td>0.4884</td>
</tr>
<tr>
<td>CSF Proteins: mean (range) in mg/dl</td>
<td>73 (24 - 647)</td>
<td>61 (20 - 425)</td>
<td>0.2584</td>
</tr>
<tr>
<td>Mental status: Altered: number (%)</td>
<td>14 (33%)</td>
<td>13 (26%)</td>
<td>0.6966</td>
</tr>
<tr>
<td>Symptoms and signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache present: number (%)</td>
<td>38 (90.5%)</td>
<td>41 (83.7%)</td>
<td>0.0520</td>
</tr>
<tr>
<td>Fever present: number (%)</td>
<td>13 (31%)</td>
<td>16 (33%)</td>
<td>0.5963</td>
</tr>
<tr>
<td>Meningism: number (%)</td>
<td>22 (52.4%)</td>
<td>19 (38.8%)</td>
<td>0.3769</td>
</tr>
<tr>
<td>Focal neurologic deficits: number (%)</td>
<td>7 (16.7%)</td>
<td>5 (10.2%)</td>
<td>0.4472</td>
</tr>
</tbody>
</table>

*1: CD4+ count was available for 13 patients in the amphotericin group and 11 patients in the fluconazole group.
## Two Weeks Clinical and Mycological Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amphotericin B group</th>
<th>Fluconazole group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mycological:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conversion of Positive CSF culture to Negative</td>
<td>16/17 (94%)</td>
<td>9/14 (64.3%)</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Clinical:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache present: no (%)</td>
<td>5/42 (12%)</td>
<td>9/49 (18%)</td>
<td>0.252</td>
</tr>
<tr>
<td>Fever present: no (%)</td>
<td>0/42 (0%)</td>
<td>2/49 (4%)</td>
<td>0.739</td>
</tr>
<tr>
<td>Meningism: no (%)</td>
<td>1/42 (2.4%)</td>
<td>3/49 (2.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Combined clinical response</td>
<td>32/42 (76%)</td>
<td>25/49 (51%)</td>
<td>0.0115</td>
</tr>
<tr>
<td>Combined clinical and mycological response</td>
<td>31/42 (73.8%)</td>
<td>22/49 (45%)</td>
<td>0.0101</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Unchanged/ improved</td>
<td>13/14 (~93%)</td>
<td>11/13 (~85%)</td>
<td>0.279</td>
</tr>
<tr>
<td>ii. Worse</td>
<td>1/14 (~7%)</td>
<td>2/13 (~15%)</td>
<td>0.279</td>
</tr>
<tr>
<td>Deaths within first 14 days</td>
<td>4/42 (9.5%)</td>
<td>10/49 (20.4%)</td>
<td>0.1513</td>
</tr>
</tbody>
</table>
### Predictors of conversion of positive CSF culture to negative, two (2) weeks after initiating antifungal treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of fever</td>
<td>1.915 (0.142 – 25.847)</td>
<td>0.624</td>
</tr>
<tr>
<td>Negative CSF Indian ink</td>
<td>0.414 (0.045 – 3.770)</td>
<td>0.434</td>
</tr>
<tr>
<td>Treatment with amphotericin B</td>
<td>6.357 (1.092 – 37.000)</td>
<td>0.019</td>
</tr>
<tr>
<td>Initial CD4 count &gt; 50cell/L</td>
<td>0.999 (0.977 - 1.021)</td>
<td>0.924</td>
</tr>
<tr>
<td>Normal initial CSF glucose &gt; 2.5mmol/L</td>
<td>0.305 (0.065 - 1.443)</td>
<td>0.134</td>
</tr>
<tr>
<td>Normal initial CSF proteins</td>
<td>0.988 (0.970 – 1.007)</td>
<td>0.206</td>
</tr>
</tbody>
</table>
PREDICTORS OF ACUTE MORTALITY IN HIV-INFECTED PATIENTS PRESENTING WITH 1\textsuperscript{ST} EPISODE CRYPTOCOCCAL MENINGITIS AT MTRH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial altered mental status</td>
<td>1.38 (0.56 – 3.41)</td>
<td>0.4788</td>
</tr>
<tr>
<td>Initial negative CSF Indian ink</td>
<td>0.79 (0.33 – 1.87)</td>
<td>0.5903</td>
</tr>
<tr>
<td>Initial positive CSF culture</td>
<td>1.70 (0.71 - 4.07)</td>
<td>0.2322</td>
</tr>
<tr>
<td>Initial treatment with amphotericin B</td>
<td>0.73 (0.4 – 1.32)</td>
<td>0.2994</td>
</tr>
<tr>
<td>Initial treatment with Fluconazole</td>
<td>1.03 (0.43 - 2.48)</td>
<td>0.9451</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.38 (0.58 - 3.25)</td>
<td>0.4620</td>
</tr>
</tbody>
</table>
ADVERSE EVENTS

- In ampho. B only
  - Chills and rigors – 23/42 (55%)
  - Increase in creat. 3/42 (7%)
  - Low potassium. 2/42(4.8%)
DISCUSSION

- Frequency of crypto meningitis; HIV-infected with neurol. Findings (34%) July 2007 to February 2008.

- No significant difference from SSA estimates

- Methodological difference with the KNH studies; 5.2-5.3%

- Higher than 12% initially reported at MTRH
TWO WEEKS TREATMENT OUTCOME

- **Clinical**: 76% vs. 51% in the ampho / FLC (p=0.0115)
  
  - Similar to findings from other studies

- **Mycological** success; 94% vs 64.5% (p=0.019). Higher than what documented; short duration of incubation

- **Combined**: 73.8% vs 45% (p=0.035)
DISCUSSION

- Acute mortality: overall 15.4. (west 5-15%)
  - Ampho. Grp- 9.5%, FLC 20.4% (p= 0.109)
PREDICTORS OF OUTCOME

- clinical & mycological success; ampho. B (p=0.019)

- Acute mortality: none; Had small numbers
CONCLUSION

- Clinical and mycological outcomes better in patients treated with ampho. B
- Acute mortality lower in ampho. B
RECOMMENDATION

- Hospital to procure & recommend use of amphotericin B during induction
LIMITATION

- Short incubation period for fungal cultures
REFERENCES


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