

FLUCYTOSINE PLUS HIGH DOSE FLUCONAZOLE IS SUPERIOR TO HIGH DOSE FLUCONAZOLE ALONE: RESULTS OF

A RANDOMIZED TRIAL COMPARING CRYPTOCOCCAL MENINGITIS TREATMENTS IN MALAWI

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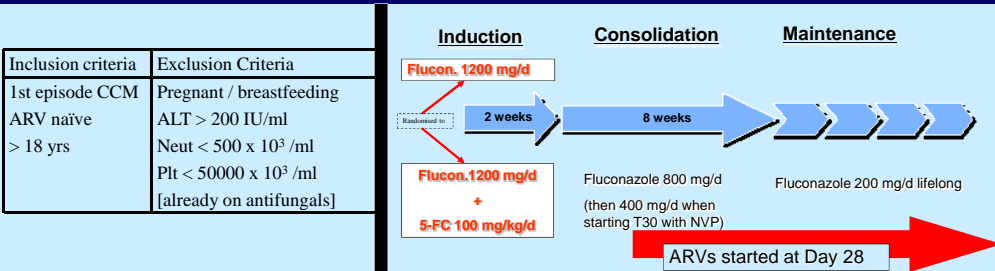
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Introduction

Cryptococcal meningitis is a major cause of HIV-associated morbidity and mortality in Africa, estimated to kill 500,000 people/year.[1] It is the commonest cause of meningitis in many parts of Sub-Saharan Africa.[2, 3, 4] Optimal treatment regimens involve the use of 2 regimens of amphotericin B, which is neither available nor feasible in most centres in Sub-Saharan Africa. Improved oral treatment regimens are needed as current treatments in the developing world have a 10 week mortality of up to 70%.[1] Fluconazole 1200mg/day is more rapidly fungicidal than 800 mg/day.[5] Therefore we examined the added benefit of adding oral flucytosine to fluconazole 1200 mg/day on the treatment of cryptococcal meningitis.

- Objectives:**
- 1) [Primary] To determine whether adding flucytosine to high-dose fluconazole in the first 2 weeks of cryptococcal meningitis treatment improves the killing of organism in the cerebrospinal fluid (EFA)
 - 2) [Secondary] Mortality and Grade III and IV Adverse Events

Methods

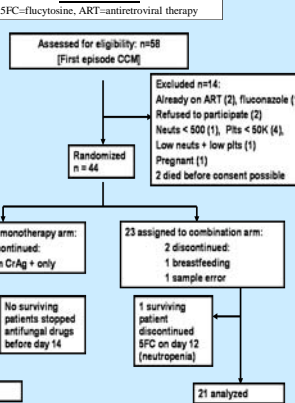


Quantitative cultures/Early Fungicidal Activity (EFA):

LPs performed Days 1, 3, 7, 14 (other days if clinically indicated). CSF plated in serial ten-fold dilution. The dilution with the least colonies, but at least 30 CFU per 200 µl, was used to calculate CFU/ml. EFA was calculated using the slope of the linear regression of log CFU/ml against time for each patient. [EFA has been shown to be independently associated with 2 and 10 week survival][6]

Results

Trial Profile



Baseline characteristics

	All patients (41)	Fluconazole monotherapy (20)	Fluconazole/5FC combination (21)	p
Clinical data				
Male (%)	27 (66%)	14 (70%)	13 (62%)	0.41
Age (years)	36 (23 – 73)	36.5 (27 – 71)	36 (23 – 73)	0.30
Mean weight in kg (standard deviation)	54.3 (12)	53.7 (14)	54.8 (10)	0.52
GCS < 15	16 (39%)	8 (40%)	8 (38%)	0.57
Taking TB meds	10 (24%)	4 (20%)	6 (29%)	0.39
Lab data				
CD4 count (x 10 ⁶ /L)	21 (1 – 101)	25 (1 – 66)	19 (3 – 101)	0.67
HIV viral load (cpm)	99,097 (2,258 – 1,145,572)	84,411 (2258 – 1,606,740)	99,442 (4,885 – 1,145,572)	0.96
CSF data				
Opening pressure (cm H ₂ O)	34 (1 – 100)	18 (1 – 100)	35 (7 – 53)	0.24
CSF white cell count/ml	11 (0 – 1307)	15 (0 – 318)	8 (0 – 1307)	0.51
QCC (CFU/ml CSF)	185,000 (265 – 30,950,000)	200,000 (265 – 30,950,000)	165,000 (1035 – 4,300,000)	0.97

Mortality and Morbidity

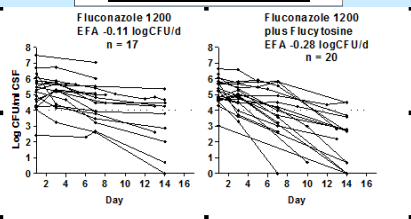
Cause of Death

	Fluconazole monotherapy		Fluconazole + Flucytosine	
	<2 wks	2-10 wks	<2 wks	2-10 wks
Cryptococcal meningitis-related	5	2	2	2
Other Infection	2	2	0	3
Pulmonary KS	0	0	0	1
Unknown	0	0	0	1

Adverse Events in first 2 weeks

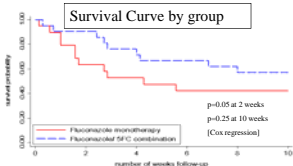
Type/Grade of event	Fluconazole monotherapy		Fluconazole + 5FC	
	Grade III	Grade IV	Grade III	Grade IV
Thrombocytopenia	1	0	1	0
Neutropenia	1	0	2	3
Anemia	1	0	1	0
Transaminase elevation	0	0	0	0
Hyponatremia	1	1	1	1
Renal failure	0	2	1	0
Total	4	4	6	4

Early Fungicidal Activity



EARLY FUNGICIDAL ACTIVITY RESULTS (mean ± SD):

- 0.11 ± 0.095 log CFU/ml/d for monotherapy
- 0.28 ± 0.17 log CFU/ml/d for fluconazole plus 5FC
- Difference = 0.18 (95% CI 0.085 – 0.27) log CFU/ml/d (p=0.0005)



Discussion and Conclusions

- Flucytosine (100 mg/kg/d) added to fluconazole 1200 mg/d lead to a marked and significant increase in rate of clearance of infection. [Accepting the limitations of comparisons between trials, the EFA of this combination (-0.28 log CFU/ml/d) is the closest an oral regimen has come to the fungicidal activity of AmB (-0.31 log CFU/ml/d for AmB 0.7 mg/kg monotherapy in Thailand)[7]]
- There was an association between EFA and survival with a strong trend to improved mortality in the combination arm.
- Neutropenia was more frequent in the combination arm but this was rarely clinically significant and rarely limited treatment
- Until intravenous amphotericin B becomes feasible in developing world setting our results argue that wider access to flucytosine should be a priority in resource limited settings.

References

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