

EBM Conference: Michelle Paulson
2/6/04

Background: *Cryptococcus neoformans* is a yeast that tends to infect immunosuppressed people, including those who are HIV-positive. Although it is possible to have disseminated disease, it usually targets the central nervous system, manifesting as meningitis. With the significant mortality associated with the infection (reported up to 25%) and incidence, it is an opportunistic infection that will likely be encountered.

Study: Van der Horst, C. *et al.* Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *New England Journal of Medicine* 337: 15-21.

Hypotheses:

1. Amphotericin at 0.7 mg/kg (higher dosing) plus flucytosine would be a superior treatment to previous doses or other medical regimens for cryptococcal meningitis
2. Fluconazole would provide at least a 15% higher success rate than itraconazole when looking at clinical and laboratory outcomes

Design: Randomized double-blind multicenter trial

Step 1: "Induction Therapy"—patients received amphotericin B 0.7 mg/kg/day and randomized to either flucytosine 100 mg/kg/day vs. placebo as the initial treatment for 2 weeks

Step 2: "Consolidation Therapy"—of the clinically stable patients from step 1, randomized to either 8 weeks of either fluconazole 400 mg/day or itraconazole 400 mg/day

Population: HIV positive patients with first episode of cryptococcal meningitis

Inclusion Criteria: HIV+ or AIDS defining illness, age 13+, 1st episode of crypto meningitis with documented +CSF culture

Exclusion Criteria: Previous ampho (>1mg/kg) or fluconazole/itraconazole/ketoconazole (>1200mg), coma, taking meds such as phenytoin, carbamazepine, phenobarb, rifamycins, or H2 blockers because of potential azole drug reactions, pregnant/lactating pts, inability to take po, hydrocortisone dosing greater than 50mg/day, active hepatitis or moderate-severe hematologic, renal or hepatic dysfunction, or any concurrent opportunist infection

definitions of heme, renal and hepatic "dysfunction" not given, so for example, then can't conclude that this study would be applicable for example, a pt w/creatinine of 1.8 baseline
lots of patients were eliminated on the basis of other medicines they were receiving, notably several antiepileptics and rifamycins...often these are common meds, esp phenytoin in the crypto patient that has seizing from their disease

Step 1: 408 enrolled, 381 eligible⇒202 amphotericin B + flucytosine
⇒179 amphotericin B alone

(both groups were very similar at baseline, see table 1—but they fail to mention viral loads and if pts were concurrently on HAART)

Step 2: 306 eligible⇒151 fluconazole
⇒155 itraconazole

***the study doesn't specifically comment on how step pts were randomized, we assume they were, but details lacking*

(both groups were also very similar at baseline, see table 2)

paper did a good job in explaining why the 75 patients from step 1 were not included in the step 2 study

Validity: YES! Pts randomized blindly (although specific details about blinding process not provided), very similar in baseline characteristics in each treatment group.

Outcomes: examined at the end of 2 weeks and 10 weeks:

- CSF cultures (+ or -) *Negative CSF is nice, but what does that really imply for the patient?*
- Symptoms
- Mini-Mental State Examination
- Combined mycologic / clinical responses

Results:

After 2 weeks, CSF was negative in 60% with both ampho and flucytosine vs. 51% with ampho only (P=0.06)

Note that this is NOT a significant difference, as the study methods define alpha level of 0.05 Interestingly, they included pts without data as +CSF and worse outcomes. (see footnotes table 3 and 4)

Clinical endpoints were not significantly different between groups

After 10 weeks, CSF was negative in 72% of the fluconazole group compared with 60% of the itraconazole group, for a difference of 12% (95%CI for the difference was -100 to 21)

That's a very large confidence interval; if they had a larger sample size in this part of the study, would it have made it easier to see a significant difference?

ALSO how do we know that they were compliant with therapy?

Clinical endpoints were again not significantly different between the groups

*There was no significant difference in any of the four combinations in terms of CSF sterilization, clinical symptoms or survival at 10 weeks

Deaths

- During initial 2 weeks, 10 of 179 pts in ampho B + flucytosine and 11 of 202 in ampho B group died for P=0.65
- During weeks 3-10, 4 of 151 fluconazole pt died compared with 8 of 155 itraconazole pts for P=0.27

***The paper describes a majority of mortality, especially early in the disease is secondary to increased intracranial pressure; the paper comments on CSF opening pressure, but then compares opening pressures of negative culture with positive cultures, which was significant (P=0.01), but did not break down the opening pressures into treatment groups...not clear why not...AND in the conclusion section, they mention a protocol used in this study for elevated ICP, but they do not give details on how many received this*

Multivariate analysis for negative CSF culture was performed:

Details of the multivariate analysis not given...

The following factors were associated with a negative culture *at 2 weeks*:

- Elevated creatinine at baseline
- Fever
- Treatment with ampho B plus flucytosine
- Negative blood cultures

No explanation given for why elevated creatinine/fever were associated with a negative culture

Doesn't say how many independent variables they analyzed...if you analysis many, one will be significant by chance alone...were they fishing for a positive association between ampho/5FC and neg cultx?

The following factors were associated with a negative culture *at 10 weeks*:

- Non IV drug user
- Negative CSF at 2 weeks
- Fluconazole use

The results for the multivariate analysis were all done using ODDS RATIOS. OR is defined as the proportion of pts with an event divided by the proportion of pts without the event. If $OR < 1$, then decreased odds and vice versa. Usually odds ratio is used in case-controlled studies. Most studies report the results as relative risk (number of people who have an outcome divided by all those who could have that outcome). Relative risk and odds ratios are similar if the outcome is RARE.

No significant difference in toxicity between amphotericin B and amphotericin B + flucytosine

AUTHORS CONCLUSION: The authors conclude that amphotericin B + flucytosine was associated with a better outcome in the multivariate analysis (*the comment doesn't say what outcome, but from the paper, one has to assume they mean negative CSF*) without any increase in side effects; (*if one uses the univariate analysis, then the outcome of negative CSF could be from chance alone*); they were unable to reject their null hypothesis that fluconazole was 15% more effective than itraconazole, and because the multivariate analysis also showed fluconazole was associated with negative CSF culture, the authors advocate amphotericin B + flucytosine followed by fluconazole. Authors also allude to the relatively low mortality rate in their study, as compared to previous studies, (*but we know nothing about the other studies, for example, comatose pts were excluded, but if included in the other studies, then my logical guess is those groups would have increased mortality*).

MY CONCLUSION: Amphotericin B + flucytosine had a *trend* toward improved outcome, as defined by negative CSF culture. There was no *increased* mortality, so at least no harm. While this study did show lower mortality than other studies, one can't directly compare them and conclude that the decreased mortality is secondary to the treatment. So overall, much less convincing evidence than one would expect. These recommendations became the guidelines in treating cryptococcal meningitis in HIV; were people eager to accept the results because the trend towards a benefit in a disease with a fair amount of mortality with little side effects? There is no clear clinical benefit, yet standard of care.

Relevance to Us:

Will it help me care for my patients? *Yes, I will accept a treatment that has little toxicity, which may be better for earlier sterile CSF cultures. Some of my patients would've been excluded however, on the basis of labs, co-infections.*

Of Note: A secondary, retrospective analysis was done from the same study, which looked at increased intracranial pressure (*Intracranial pressure measurements were not required in the study, and of the 381 pts from step I, only 221 had opening pressure done*). Of the patients who had ICP measured, 60% were above 250 mmHg and 30% were above 350 mmHg. They evaluated patients who had opening pressures done, arbitrarily placed them in 4 groups based on the opening pressure. They found an association of ICP > 350 mmHg with papilloedema, hearing loss, crypto titers, and % of positive India ink smears. Because only 21 patients died and only 12 had opening pressures measured, no clear association could be made with mortality.

From: Graybill, JR *et al.* Diagnosis and Management of Increased Intracranial Pressure in Patients with AIDS and Cryptococcal Meningitis. *Clinical Infectious Diseases* 2000; 47-54.