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# Is early fungicidal activity a surrogate marker for mortality in the evaluation of antifungal therapies in HIV-associated cryptococcal meningitis ?

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*Background*: Early fungicidal activity (EFA), i.e. the CSF clearance rate of quantitative yeast culture colony counts during the first 14 days of antifungal therapy, is often used as the primary endpoint in phase II trials in HIV-associated cryptococcal meningitis. While associations between EFA and survival have been reported, it is unclear whether EFA is a surrogate marker.

*Methods*: Data from eight randomized controlled trials and four cohort studies from Asia and Africa (23 distinct treatment and study combinations) were pooled. EFA was estimated based on a linear mixed effects model of the longitudinal log10-CSF Cryptococcus colony forming unit (CFU) counts treating values below the detection limit as left-censored. Ten-week risks of death were estimated with the Kaplan-Meier method.

*Results*: Data from 976 subjects contributing a total of 2851 quantitative culture measurements were included. Median EFA and 10-week risks of death were ¬ 0.13 log10 CFU/ml/day and 55% for fluconazole monotherapy (n=80), 0.27 and 43% for fluconazole/flucytosine combinations (n=21), 0.35 and 38% for amphotericin B monotherapy (n=152), 0.35 and 36% for amphotericin B/azole combinations (n=441), 0.49 and 26% for amphotericin B/flucytosine combinations (n=224), and 0.58 and 30% for amphotericin B/flucytosine/interferon-gamma combinations (n=58). There was a positive correlation between faster EFA and 10-week mortality across treatment/study combinations (R2=0.44, 95%CI: 0.14-0.71). However, correlation between observed treatment effects on EFA and 10-week mortality from randomized clinical trials (R2trial=0.04, 95%CI: 0.00-0.47; n=620), and average correlations between an individuals' EFA and survival time within treatment/study combinations (average squared Somers' rank correlation R2indiv=0.07, 95%CI: 0.04-0.11) were low.

*Conclusion*: EFA remains a useful marker of antifungal activity but surrogacy for 10-week mortality could not be established. Limitations of this study are that azole and azole combination treatments were more often used in the most resource-limited settings, and that only one of the included antifungal trials was powered for mortality.

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