CORRESPONDENCE

Combination Antifungal Therapy for Cryptococcal Meningitis

TO THE EDITOR: In the trial of combination therapy for cryptococcal meningitis in patients with human immunodeficiency virus infection, Day et al. (April 4 issue)[1] found a survival benefit associated with 2 weeks of therapy with amphotericin B and flucytosine as compared with amphotericin B monotherapy. The results of this trial reinforce the treatment combination as the standard per current guidelines.[2,3] In locations where amphotericin B therapy is not feasible, flucytosine is recommended in combination with fluconazole.[2-4] However, the availability of flucytosine worldwide remains grossly inadequate.

Flucytosine is currently unregistered and unavailable in most of Asia and Africa, where the disease burden is greatest.[5] Even though flucytosine is a simple, orally administered, off-patent drug, only two manufacturers have been approved by the Food and Drug Administration: the originator company, Meda Pharmaceuticals, and the generic manufacturer, Sigmapharm Laboratories. The lack of data about disease burden, concerns regarding toxicity, and high drug costs due to a lack of competition have contributed to a market failure for flucytosine.[5] Given the findings of Day et al., sustained efforts from governmental and international stakeholders are now required in order to urgently disseminate and implement World Health Organization (WHO) treatment guidelines, facilitate the registration of flucytosine, motivate generic-drug production, stimulate development of sustained-release formulations of flucytosine, and widen access to this drug.[3,5]

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No potential conflict of interest relevant to this letter was reported.

1. Day JN, Chau TTH, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med 2013;368:1291-302.
2. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010;50:291-322.
3. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization, December 2011.
4. Nussbaum JC, Jackson A, Namarika D, et al. Combination flucytosine and high dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomised trial in Malawi. Clin Infect Dis 2010;50:338-44.
5. Loyse A, Thangaraj T, Easterbrook P, et al. Cryptococcal meningitis: improving access to essential antifungal medicines in resource-poor countries. Lancet Infect Dis 2013 June 2 (Epub ahead of print).

DOI: 10.1056/NEJMc1305981

THE AUTHORS REPLY: We agree with Loyse et al. that increasing access to flucytosine could reduce deaths from cryptococcal meningitis. In

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our study, flucytosine levels were not monitored, but patients had regular blood counts and electrolyte and creatinine measurements. We showed that in a resource-constrained setting, in combination with amphotericin B, flucytosine can be used safely and increases both survival and fungal clearance. Patients receiving the combination treatment had similar rates of adverse events as those receiving amphotericin B monotherapy. Fluconazole combined with flucytosine, recommended as second-line treatment by the WHO, is an attractive treatment for cryptococcal meningitis because of ease of administration.[1] Fluconazole is cheaper than amphotericin B and has a favorable toxicity profile. However, amphotericin B–sparing combinations consistently show lower rates of yeast clearance from cerebrospinal fluid — early fungicidal activity — than those containing amphotericin B.[2] Bicanic and colleagues found that early fungicidal activity was closely correlated with survival.[3] Therefore, in addition to improving access to flucytosine, it is imperative that stakeholders work to improve the availability of, and the capacity to safely administer, amphotericin B.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization, December 2011.
2. Jackson AT, Nussbaum JC, Phulusa J, et al. A phase II randomized controlled trial adding oral flucytosine to high-dose fluconazole, with short-course amphotericin B, for cryptococcal meningitis. AIDS 2012;26:1363-70.
3. Bicanic T, Muzoora C, Brouwer AE, et al. Independent association between rate of clearance of infection and clinical outcome of HIV-associated cryptococcal meningitis: analysis of a combined cohort of 262 patients. Clin Infect Dis 2009;49:702-9.

DOI: 10.1056/NEJMc1305981

Ischemic Heart Disease after Breast Cancer Radiotherapy

TO THE EDITOR: In their analysis of ischemic heart disease in a Nordic cohort of survivors of breast cancer, Darby et al. (March 14 issue)[1] observe a significant excess relative risk associated with radiotherapy, which is concordant with the risks seen in other radiotherapy-treated groups[2,3] (Table 1). This finding suggests that the mean dose to the heart is the most relevant metric for predicting radiation-associated ischemic heart disease. The findings about the radiation risks also agree with those of a recent meta-analysis[4] of low-to-moderate radiation exposure (Table 1), implying little sparing effect of low doses and protracted radiation exposures. The comprehensive analysis by Darby et al. of other risk factors for ischemic heart disease suggests minimal interaction with radiogenic risk, again consistent with (more limited) observations reviewed elsewhere.[4]

All these findings suggest that there is excess ischemic heart disease associated with high (therapeutic) and low (diagnostic) doses of radiation. Although there has been concern about increased risks of cancer associated with computed tomographic (CT) angiograms and coronary-artery calcium scans,[6] the evidence presented by Darby et al. and elsewhere[5] strongly suggests that clinicians should also be concerned with cardiovascular morbidity and should limit the dose of radiation affecting the heart.

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No potential conflict of interest relevant to this letter was reported.

1. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987-98.