Sir—In their recent article, Fong et al. [1] report that long-term administration of high-dose acyclovir may protect against development of AIDS-related non-Hodgkin’s lymphoma (NHL). We recently examined this hypothesis in a case-control study of 219 patients with AIDS-NHL and 219 HIV-positive controls, matched for degree of immune deficiency, in Sydney, Australia [2]. Our results, in a study with >7 times as many cases as studied by Fong et al., showed no relationship between acyclovir use and risk of NHL. The same percentage of case and control subjects (5.5%) had received high-dose acyclovir (mean daily dose, ≥800 mg) during the 1-year period prior to NHL diagnosis or match date, and at lower doses there was no relationship between dose received and NHL risk. Receipt of ganciclovir in the year prior to diagnosis was nonsignificantly protective (odds ratio [OR], 0.51; 95% confidence interval [CI], 0.20–1.25). In further unpublished analyses, we found that 44% of cases and 36% of controls had received any acyclovir during the year prior to diagnosis (P = .08). There was no significant association between acyclovir or ganciclovir use and the risk of individual NHL subtypes (immunoblastic, Burkitt’s, or primary CNS lymphoma).

We believe that differences in study design may explain these discrepant results. Fong et al. [1] acknowledge that the use of prolonged high-dose acyclovir has changed over time, related to study findings in 1993 that high-dose acyclovir in combination with zidovudine prolonged life in people with AIDS [3]. Specifically, we believe that the use of high-dose acyclovir increased in the early 1990s and then decreased when effective antiretroviral therapies became available. These changes in use of acyclovir over time mean that year of diagnosis of NHL will confound relationships between acyclovir and NHL risk. Unlike our study, in which cases and controls were matched for date of diagnosis (±6 months), the study by Fong et al. [1] does not appear to be matched for date of diagnosis. A reanalysis of their results adjusted for year of diagnosis would address this concern.

Fong et al. [1] suggest that randomized controlled trials of anti-herpesviral agents are warranted, to further investigate this hypothesis. In fact, several large trials of acyclovir have been published, and a meta-analysis of these trials in a total of 1792 patients found that high-dose acyclovir did not protect from death due to NHL (OR, 0.83; 95% CI, 0.35–1.92) [4]. Individual randomized controlled trials of ganciclovir have shown that systemic therapy decreases the risk of development of Kaposi’s sarcoma [5] but not NHL [6]. A meta-analysis of ganciclovir trials is warranted, to further investigate whether systemic therapy may affect NHL risk.

The prevention of NHL in people with HIV infection is of increasing importance, since this malignancy is comprising an increasing proportion of AIDS-related illnesses [7]. However, we conclude that currently there are insufficient data to justify new randomized controlled trials of anti-herpesviral agents to prevent NHL.

Andrew E. Gruelich and Matthew G. Law
National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia

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Reprints or correspondence: Dr. Andrew Grulich, National Centre in HIV Epidemiology and Clinical Research, Level 2, 376 Victoria St., Sydney, NSW 2010, Australia (aggrulich@unrhe.unsw.edu.au).

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Comparison of Nephrotoxicity of Amphotericin B Products

Str—Winston and Schiller [1] report the results of the analysis of their institution’s data from a multicenter, randomized study that compared amphotericin B lipid complex (ABLC; The Liposome Company) with conventional amphotericin B (CAB; Apothecon) as empiric therapy for febrile neutropenic patients. They found a similar incidence of nephrotoxicity (defined as a doubling of the baseline serum creatinine concentration) and infusion-related reactions (fever and chills) in both treatment arms, which was surprising. This prompted us to undertake a detailed examination of the available data on nephrotoxicity associated with these agents.

There is little comparative data available on nephrotoxicity associated with ABLC treatment, and, therefore, it is unfortunate that Winston and Schiller’s study was prematurely discontinued by the sponsor (The Liposome Company), despite objections from the investigators. The data that we did find included the results of a comparative trial of ABLC and CAB as treatment for cryptococcal meningitis in patients with AIDS [2]. The authors of this study reported that, in the 2 treatment arms (patients who received ABLC at a dosage of 5 mg/kg/day those who received CAB at a dosage of 0.7 mg/kg/day), the mean increase in serum creatinine levels from baseline through week 1 was identical.

Wingard and colleagues [3] reported results of a double-blind comparative trial that compared ABLC (5 mg/kg/day) with lipid-associated amphotericin B (3 and 5 mg/kg/day) as empiric therapy for febrile neutropenic patients. They found that the incidence of nephrotoxicity (defined as a doubling of the baseline serum creatinine concentration) was 42% in the cohort of patients that received the amphotericin B lipid complex, 15% in the cohort that received lipid-associated amphotericin B at a dosage of 5 mg/kg/day, and 14% in the cohort that received lipid-associated amphotericin B at a dosage of 5 mg/kg/day. The result for the latter cohort was similar to that reported by Walsh and colleagues [4], who found an incidence of nephrotoxicity of 19% for patients who received a dosage of 5 mg/kg/day of lipid-associated amphotericin B and had a doubling of serum creatinine level from baseline.

To further validate the nephrotoxicity findings of Wingard and colleagues [3] with other ABLC findings, we contacted the study sponsor and requested the data for the parameters defining nephrotoxicity that were reported in the ABLC package insert ([5]; personal communication, Fujisawa HealthCare). The package insert notes that there are data for patients with increases in serum creatinine level from normal baseline to $1.5$ mg/dL and $2.0$ mg/dL. These data are derived primarily from the unpublished results of 3 randomized comparative studies of ABLC therapy at a dosage of 5 mg/kg/day. Using an increase in serum creatinine level to $1.5$ mg/dL as the definition of nephrotoxicity, the ABLC package insert calculated an incidence of 38% (47 of 124 patients) in the 3 unpublished studies, compared with an incidence of 44% in the study by Wingard and colleagues [3]. Using an increase in serum creatinine level of $2.0$ mg/dL as the definition of nephrotoxicity, the incidence was 24% in the 3 unpublished studies and 21% in the study by Wingard and colleagues [3]. Of note, the incidence of nephrotoxicity among patients who received 3 mg/kg/day of lipid-associated AmB was 19% if the 1.5 mg/dL definition was used and 10% if the 2.0 mg/dL parameter was used; among patients treated with a dosage of 3 mg/kg/day, the incidence was 16% if the 1.5 mg/dL definition was used and 5% if the 2.0 mg/dL parameter was used.

It appears that the incidence of nephrotoxicity that is associated with ABLC therapy when it is administered at the dosage approved by the US Food and Drug Administration (5 mg/kg/day) may be the same as the incidence associated with CAB therapy [5]. The results of a comparative study, such as the one which was prematurely discontinued by the ABLC’s manufacturer, would be interesting to see.

Colleen Carrigan Harrell
Lauryl Hanf-Kristufek
St. Charles Mercy Hospital, Oregon, Ohio

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