

CORRESPONDENCE



The Precursor of Chronic Lymphocytic Leukemia

TO THE EDITOR: Landgren and colleagues (Feb. 12 issue)¹ present data that cannot be used to differentiate monoclonal B-cell lymphocytosis (MBL) from chronic lymphocytic leukemia (CLL). The findings of clonal B-cell populations are based on flow-cytometric and molecular analyses, but these approaches do not measure the B-cell count in the prediagnostic blood sample. In Table 2 of the article, the values for “lymphocytes” are percentages of lymphocytes among all cells in the thawed samples measured by means of flow cytometric analysis. Both the absolute lymphocyte count and the percentage of B cells as measured by flow cytometry are mandatory for calculating the B-cell count.² Without a blood count, unrecognized CLL is the likely explanation for their findings, since it is asymptomatic in its early stage. The primary conclusion of Landgren et al. that MBL is a “precursor state” is not scientifically valid on the basis of the data presented. The issue of whether MBL has a precursor or concurrent³ relationship with CLL remains unresolved.

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1. Landgren O, Albitar M, Ma W, et al. B-cell clones as early markers for chronic lymphocytic leukemia. *N Engl J Med* 2009;360:659-67.

2. Mulligan CS, Thomas ME, Mulligan SP. Lymphocytes, B-lymphocytes and clonal CLL cells: impact of the new diagnostic criteria in the 2008 guidelines for chronic lymphocytic leukemia (CLL). *Blood* (in press).

3. *Idem*. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. *N Engl J Med* 2008;359:2065-6.

THE AUTHORS REPLY: The point that Mulligan and colleagues raise is addressed in our article. Although a complete blood count was not included in the baseline blood-test panel in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, we are confident of our results, for several reasons. First, in 16 of 45 patients (36%), the number of circulating lymphocytes (CD19+ and CD5+ B cells) was negligible ($\leq 1\%$) or low (>1 to 20%), accounting for 6% or less of all lymphocytes; this makes it very unlikely that a diagnostic B-cell lymphocytosis was already present. Second, about 90% of the cases of CLL that we detected were as early as Rai stage 0 or I, which is consistent with regular health evaluations in these patients (in the 3 years before enrollment, 38 of 45 patients [84%] underwent some screening study). Third, our study population is a health-conscious group that volunteered for annual screening; the compliance of these patients was in accordance with the requirements of the PLCO trial.¹

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Although we cannot totally exclude the possibility that CLL existed before the date of diagnosis in a few patients, it is highly unlikely that CLL would remain undiscovered for years in this intensively screened group. The data are entirely consistent with our contention that CLL often has a precursor state.

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Anti-Interleukin-5 Therapy and Severe Asthma

TO THE EDITOR: Haldar and coworkers (March 5 issue)¹ report a significant reduction of severe exacerbations of asthma after eosinophil suppression with mepolizumab in a population of patients with severe, refractory asthma in Leicestershire, United Kingdom. However, patients receiving mepolizumab still had a mean of 2.0 severe exacerbations per year.¹ Could this excess be due to air pollution, since exposure to small particles is strongly linked to exacerbations of asthma?² The Web site of the Leicester City Council provides 24-hour monitoring of particle concentrations that are less than 10 μm in aerodynamic diameter (PM_{10}) in the urban Leicester area.³ According to our calculations, during the study period (from April 1, 2006, through August 31, 2008, a total of 884 days), the mean 24-hour PM_{10} concentrations exceeded the maximum air-quality guidelines of the World Health Organization⁴ (50 μg per cubic meter) a total of 230 times in three of eight measurement sites located along the Leicester motorway system. Given the effective suppression of eosinophilic inflammation reported in the study by Haldar et al., their data combined with those from the Leicester Web site provide a unique opportunity for assessment of the magnitude of air-pollution-induced exacerbations of asthma,⁵ which still remains unknown.

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2. Leicester Air Quality Monitoring Network. Leicester, UK: Leicester City Council. (Accessed May 21, 2009, at <http://rcweb.leicester.gov.uk/pollution/asp/home.asp>.)

3. Künzli N, Perez L, Lurmann F, Hricko A, Penfold B, McDonnell R. An attributable risk model for exposures assumed to cause both chronic disease and its exacerbations. *Epidemiology* 2008;19:179-85.

4. Air quality guidelines: global update. Geneva: World Health Organization, 2005:217-80.

5. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med* 2007;357:2348-58.

TO THE EDITOR: The articles by Haldar et al. and Nair et al.¹ indicate that mepolizumab has positive therapeutic effects in selected patients with refractory eosinophilic asthma and frequent exacerbations despite treatment with corticosteroids. Since previous clinical trials involving patients with less severe asthma have not shown efficacy, the heterogeneity in the biologic response to the drug might depend on the phenotype of asthma. The patients in the studies by Haldar et al. and Nair et al. had a difficult-to-treat, eosinophilic asthma with an onset in the patients' mid-20s; 30 to 40% of them had nasal polyps. This phenotype is reminiscent of aspirin-sensitive asthma.^{2,3} I wonder, therefore, whether the patients underwent aspirin-provocation testing and, if not, whether they had a history of intolerance to nonsteroidal antiinflammatory drugs.

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