To the Editor:

In an Editorial in the April 15, 1993 issue of Blood,1 Le Beau discusses the indisputable value of fluorescence in situ hybridization (FISH) for the analysis of genetic changes in leukemia cells. We would like to comment on a number of the statements concerning chronic lymphocytic leukemia (CLL). Le Beau states that by cytogenetic analysis, approximately 50% of the cases are inadequate and, of the remaining cases, one-half appear to have normal karyotype and 15% to 20% have trisomy 12. The detection of chromosome abnormalities by cytogenetics is dependent on the technique, mainly regarding the activation of CLL cells in culture. When we analyzed the data from the International Working party on Chromosomes in CLL (IWCCLL), together with chromosome studies published from other groups, the overall incidence of clonal abnormalities was 43% (533 of 1,244 cases studied). Some laboratories identified clonal abnormalities in more than 50% of their cases. Trisomy 12 was found in one-third of those with clonal abnormalities and 13q abnormalities (mostly deletions) were found in 20%. Small interstitial deletions of 13q may be missed in less than optimal quality preparations, and some laboratories have identified 13q deletions in one-third of their cases (reviewed by Juliusson and Gahrton3). It is not correct to say that the prognostic value of trisomy 12 detected by cytogenetics is inconclusive. Patients with trisomy 12 have a poorer prognosis than those with a normal karyotype, 13q deletions, or single abnormalities involving other chromosomes. However, because the impact of trisomy 12 on survival is weak, large studies were required to show any statistical significance. The FISH technique is clearly an important tool in identifying abnormalities in patients whose leukemic cells resist mitogen activation in vitro. However, it fails to identify multiple chromosomal abnormalities, which are a better marker for poor prognosis than the detection of trisomy 12 alone.

Le Beau quotes the report of Stilgenbauer et al,8 which describes the use of FISH to detect monoallelic loss of the RB1 gene in CLL, as a “pivotal study.” The high frequency of 13q14 abnormalities in CLL was first documented by Fitchett et al in 1987.9 This has repeatedly been confirmed,10,11 eg, in the IWCCLL study,2 which also identified a prognostic impact of this genetic change. Accordingly, several studies then showed RB1 gene deletions by molecular techniques,12,13 both in patients with 13q14 deletions and in those with normal karyotypes. However, both RB1 alleles have not been shown to be inactivated.12 We think that the RB1 gene deletion is an innocent bystander in CLL. Of greater interest is the recent finding that the D13S25 probe identifies a region located telomeric to the RB1 gene, which may be homozygously deleted in CLL,12,14 and may indicate a new tumor suppressor gene relevant for the pathogenesis of CLL.
REFERENCES


Chromosome abnormalities and RB1 gene deletions in chronic lymphocytic leukemia [letter; comment]

G Juliusson, G Gahrton, S Einhorn, Y Liu, DG Oscier and R Chapman