with stage IV-A bone marrow–positive FL 3.5 years after enrollment.

Sequencing of the translocation breakpoint confirmed a clonal relationship between the translocation found in prediagnostic blood and that present in the tumor. Subsequent observation of the lymphoma allowed us to estimate a doubling time of approximately 1 year based on enlargement of a radiologically evident inguinal lymph node suggesting that t(14;18) positive cells detectable in prediagnostic blood may have been from the as yet undetected lymphoma. No other controls in this study possessed abnormally elevated levels of t(14;18)-positive cells.

Regardless of whether circulating t(14;18) positive cells in the prediagnosis peripheral blood from this patient were predictive of her subsequent development of FL or an indicator of undetected early disease, this finding highlights the potential for use of t(14;18) levels in peripheral blood as a screening tool for those at elevated risk of FL. Further research, including t(14;18) testing of participants in large cohort studies, will be necessary to confirm and characterize this relationship.

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References

To the editor:

The prognostic value of multilineage dysplasia in de novo acute myeloid leukemia patients with intermediate-risk cytogenetics is dependent on NPM1 mutational status

The prognostic significance of multilineage dysplasia (MLD) in acute myeloid leukemia patients with intermediate-risk cytogenetics (IR-AML) presenting as de novo disease is unclear.1-4 Falini et al have recently analyzed the biologic and prognostic significance of MLD in IR-AML and did not find any impact of MLD on survival in patients harboring NPM1 mutations.5 Moreover, in a subgroup of IR-AML patients with wild-type NPM1 from one of the participating institutions (Munich Leukemia Laboratory), no difference in outcome according to the presence of dysplastic features was observed. To clarify the prognostic significance of MLD in this cytogenetic category, we analyzed a cohort of 130 patients (51% female; median age, 53 years, range, 18-74 years) diagnosed consecutively with de novo IR-AML in our institution from 1994 to March 2010 and treated with intensive chemotherapy. Evaluation of dysplasia was performed by 2 independent observers (M.R., J.Ll.A.) according to the WHO criteria.2

Figure 1. Survival curves of patients up to 60 years with intermediate-risk cytogenetics AML depending on NPM1 status and presence of multilineage dysplastic features (MLD). (A) In NPM1-mutated AML, no significant differences in OS were observed between cases with (discontinuous line) and without (continuous line) MLD (P = .97). (B) On the contrary, MLD identified a subgroup of patients with an adverse outcome among wild-type NPM1 IR-AML (P = .012).
Multilineage dysplasia was detected in 32 cases (25%), a frequency similar to that reported by Falini, and was associated with a higher proportion of normal karyotype (93% vs 60%; \( P < .001 \)), lower leukocyte count at diagnosis (32 \( \times 10^9/L \) vs 69 \( \times 10^9/L \); \( P = .01 \)), and lower bone marrow infiltration (51% vs 72% blast cells, \( P < .001 \)). Interestingly, the frequency of NPM1 and FLT3 internal tandem duplication (FLT3-ITD) mutations did not differ between patients with and without MLD (59% vs 50%, and 31% vs 38%, respectively). NPM1 mutations were found in 68 patients (52%). MLD was observed in 19 patients (28%) with mutated NPM1 and in 13 (21%) with wild-type NPM1. Outcomes in patients with mutated NPM1 were similar for those with and without MLD; response rate was 95% and 85%, 5-year relapse incidence was 35% \( \pm 26\% \) and 47% \( \pm 16\% \), and 5-year survival was 56% \( \pm 23\% \) and 46% \( \pm 14\% \), respectively. In contrast in patients with wild-type NPM1, those patients with MLD showed an inferior response rate to induction chemotherapy (53% vs 85%; \( P = .02 \)). When the analysis was restricted to younger patients (\( \leq 60\) years) those with MLD showed a lower 5-year survival (0% vs 40% \( \pm 16\% \); \( P = .012 \); Figure 1). The unfavorable prognostic value of MLD on response rate (\( P = .034 \); relative risk, 4.8; 95% confidence interval, 1.1-20) and survival (\( P = .036 \); hazard ratio = 2.5; 95% confidence interval, 1.1-6) was confirmed in a multivariate analysis.

These results confirm that, although dysplastic features are a common trait in NPM1-mutated AML, they do not confer a worse prognosis. Falini et al found that expression profiling did not identify any distinctive MLD-associated gene signature in the mutated NPM1 cohort.\(^1\) The correlation found in the present study between an unfavorable outcome and dysplastic features in wild-type NPM1 IR-AML patients leads us to suggest that a search for novel genetic or epigenetic markers in this AML subgroup might reveal a specific biologic identity.

In conclusion, the prognostic relevance of MLD in IR-AML might be dependent on NPM1 mutational status. Whereas MLD predicts an adverse outcome in patients with wild-type NPM1, it lacks prognostic value in NPM1-mutated AML. Nonetheless, this observation requires further confirmation in a larger series of patients.

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References

To the editor:

Platelet secretion defect in patients with familial hemophagocytic lymphohistiocytosis type 5 (FHL-5)

Familial hemophagocytic lymphohistiocytosis (FHL) is a genetic disorder of lymphocyte cytotoxicity caused by mutations in the gene encoding perforin (FHL-2) or in genes encoding proteins important for intracellular trafficking and exocytosis of perforin-containing lytic granules.\(^1\) These include Munc13-4 (FHL-3), syntaxin 11 (FHL-4), and Munc18-2 (FHL-5). The molecular

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