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Residual Clones in Childhood Leukemia

To the Editor: Roberts and his colleagues (Jan. 30 issue)¹ do not emphasize that childhood acute lymphoblastic leukemia (ALL) is a heterogeneous disease with different rates of elimination of blast cells. The kinetics of the decrease in the minimal residual disease and the level of minimal residual disease that is compatible with a cure may differ among the leukemias and among the cytogenetic or immunophenotypic subtypes of childhood ALL.

For example, of six patients with a first complete remission of t(1;19)-positive ALL, five had molecular remissions within 3 months, and one had minimal residual disease after 84 months of complete remission.² In another study,³ all five long-term survivors with t(1;14)-positive ALL were consistently negative for minimal residual disease after the completion of induction therapy, whereas all seven patients who were consistently positive for minimal residual disease had resistant disease or had had relapses. In children with Philadelphia chromosome–positive ALL, *BCR–ABL* fusion transcripts may be undetectable throughout the period of complete remission, with a reversion to positive findings before a clinical relapse occurs.^{4,5} In a recent study, the *TEL–AML1* fusion transcripts, which may be detected in about 20 percent of patients with B-lineage ALL and are associated with a good prognosis, were undetectable in two of nine patients after induction therapy and in three of four after a follow-up of more than 200 days.⁶

Detailed information on the immunologic and cytogenetic features of the cases reported by Roberts et al. would have helped in interpreting their data. Discrepancies among studies, together with the complexity of the methods used, do not justify the use of the polymerase-chain-reaction (PCR) assay for routine monitoring.

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References

1. Roberts WM, Estrov Z, Ouspenskaia MV, Johnston DA, McClain KL, Zipf TF. Measurement of residual leukemia during remission in childhood acute lymphoblastic leukemia. *N Engl J Med* 1997;336:317-323. [[Abstract/Full Text](#)]
2. Privitera E, Rivolta A, Ronchetti D, Mosna G, Giudici G, Biondi A. Reverse transcriptase/polymerase chain reaction follow-up and minimal residual disease detection in t (1;19)-positive acute lymphoblastic leukaemia. *Br J Haematol* 1996;92:653-658. [[Medline](#)]
3. Cimino G, Elia L, Rivolta A, et al. Clinical relevance of residual disease monitoring by polymerase chain reaction in patients with ALL-1/AF-4 positive-acute lymphoblastic leukaemia. *Br J Haematol* 1996;92:659-664. [[Medline](#)]
4. Miyamura K, Tanimoto M, Morishima Y, et al. Detection of Philadelphia chromosome-positive acute lymphoblastic leukemia by polymerase chain reaction: possible eradication of minimal residual disease by marrow transplantation. *Blood* 1992;79:1366-1370. [[Abstract](#)]
5. Gehly GB, Bryant EM, Lee AM, Kidd PG, Thomas ED. Chimeric BCR-abl messenger RNA as a marker for minimal residual disease in patients transplanted for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 1991;78:458-465. [[Abstract](#)]
6. Cayuela JM, Baruchel A, Orange C, et al. TEL-AML1 fusion RNA as a new target to detect minimal residual disease in pediatric B-cell precursor acute lymphoblastic leukemia. *Blood* 1996;88:302-308. [[Abstract/Full Text](#)]

To the Editor: As the parent of a child undergoing treatment for ALL, I read the report by Roberts et al. with great interest. Although their efforts are to be commended, I am concerned about their conclusion and its potential effect on the treatment of ALL.

The authors concluded that clonal eradication may not be a prerequisite for a cure. There are several problems with this conclusion. First, the authors applied relapse rates from other trials to their trial as a way of predicting how many of the children they treated would have relapses. As Pui et al.¹ demonstrated, patterns of relapse can differ from one treatment protocol to another. It is possible that the authors' treatment strategy will result in an uncommonly high rate of late relapses and that the minimal residual disease detected by their PCR methods is a marker for this phenomenon. In addition, it is not certain that the cells that Roberts et al. detected were representative of the leukemic clone. As Greaves² notes in the editorial accompanying their article, the cells detected could represent a preleukemic cell population from which the leukemic clone mutated. Finally, on the basis of a review of 20 studies, Roberts et al.³ stated that the absence of minimal residual disease was correlated with an extended complete remission, whereas the persistence or reappearance of minimal residual disease was correlated with a relapse. Their conclusion contradicts this statement.

The authors' conclusion could lead to an approach in which residual disease is tolerated and treatment strategies are not sufficiently intensive to achieve a cure in a majority of patients. Unless lifelong follow-

up of children with ALL proves that clonal eradication is unnecessary, it should remain the objective of treatment and be considered synonymous with a cure.

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References

1. Pui C-H, Dodge RK, Look AT, et al. Risk of adverse events in children completing treatment for acute lymphoblastic leukemia: St. Jude total therapy studies VIII, IX, and X. *J Clin Oncol* 1991;9:1341-1347. [[Abstract](#)]
2. Greaves M. Silence of the leukemic clone. *N Engl J Med* 1997;336:367-369. [[Full Text](#)]
3. Roberts WM, Estrov Z, Kitchingman GR, Zipf TF. The clinical significance of residual disease in childhood acute lymphoblastic leukemia as detected by polymerase chain reaction amplification by antigen-receptor gene sequences. *Leuk Lymphoma* 1996;20:181-197. [[Medline](#)]

To the Editor: Roberts et al. demonstrated that clones of pre-B-lymphoblastic cells persist in bone marrow from children with ALL in clinical remission. In his accompanying editorial, Greaves suggested the potential importance of immunologic control of residual premalignant or malignant clones.

In patients with human immunodeficiency virus (HIV) infection, we have found an analogous increase in circulating lymphocytes with the t(8;14) translocation of *c-myc* characteristic of AIDS-associated Burkitt's and non-Hodgkin's lymphomas. In our prospective study of a cohort of 209 homosexual men, transient or persistent clonal *c-myc* recombinations were present in 13 of 113 subjects (12 percent) with HIV infection and 2 of 96 (2 percent) without HIV infection (relative risk, 5.5; $P < 0.001$).¹

To complement the findings of Roberts et al., we analyzed our data according to the duration of HIV infection. Clones with the t(8;14) translocation were present in 15 of 191 samples (8 percent) obtained 6 to 13 years after HIV seroconversion, as compared with 9 of 384 samples (2 percent) obtained less than 6 years after seroconversion (relative risk, 3.4; $P = 0.001$) and 2 of 398 samples (0.5 percent) from subjects without HIV infection. Most clones with the translocation were transient, but in four patients, mutant clones with unique gene sequences persisted for one to nine years in the absence of overt malignant disease.

In contrast to the residual clones in children with leukemia, *c-myc* recombinations in the HIV-infected subjects were not associated with the subsequent development of lymphoma. Lymphoma developed in 2 of the 13 HIV-infected subjects (15 percent) with recombinations, as compared with 12 of the 100 (12 percent) without recombinations (relative risk, 1.3; $P = 0.5$). Lymphoma tissue from one subject with a preceding clonal recombination had a normal germ-line *c-myc* configuration; tumor tissue from the other subject was not available for testing.

In our study, the prevalence of circulating clones with the lymphoma-associated mutation increased with prolonged HIV infection, in parallel with the risk of lymphoma.² However, even with severely impaired immunity, these clones were not associated with an increased risk of lymphoma. Greaves speculated that the malignant phenotype in ALL may require two independent mutations, an idea that recalls Knudson's "two-hit" hypothesis.³ Our data suggest that the development of B-cell lymphoma also entails a multistep process.

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References

1. Müller JR, Janz S, Goedert JJ, Potter M, Rabkin CS. Persistence of immunoglobulin heavy chain/c-myc recombination-positive lymphocyte clones in the blood of human immunodeficiency virus-infected homosexual men. *Proc Natl Acad Sci U S A* 1995;92:6577-6581. [\[Abstract\]](#)
2. Rabkin CS, Goedert JJ. Risk of non-Hodgkin lymphoma and Kaposi's sarcoma in homosexual men. *Lancet* 1990;336:248-249.
3. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A* 1971;68:820-823. [\[Medline\]](#)

The authors reply:

To the Editor: We could not find any association between immunologic or karyotypic features of leukemic lymphoblasts at the time of the diagnosis and residual leukemia during remission in the cohort of 24 patients we described in our article, but the statistical power of subgroup analyses was limited. We will evaluate minimal residual disease according to genetic subtypes of B-precursor ALL in future studies. Since the sensitivity of PCR differs for each unique fusion transcript, we will compare the amplification of rearranged immunoglobulin (IgH) gene sequences with the detection of fused sequences associated with the four most common translocations: (12;21), (1;19), (9;22), and (4;11).

As pediatricians who treat children with ALL, we share the concern that our results may guide therapeutic decisions, and we emphasize that this is premature. However, the concept that a cure in this disease may not occur by complete annihilation of leukemic cells remains valid. The finding, during long-term remission, of cells with rearranged *IgH*-gene V–D–J sequences identical to those of the lymphoblast clone at the time of the diagnosis of ALL was unexpected and appears to be the result of the increased sensitivity of our PCR assay.

Since the publication of our report, one additional patient has had a relapse, which occurred 53 months after the diagnosis. In this patient, all three bone marrow samples analyzed after the completion of

therapy were positive by PCR, but an insufficient number of cells were available to perform the blast-colony assay. As of April 1, 1997, the median time since the completion of treatment in the 16 patients who continue to be in remission was 31 months (range, 14 to 47). Although it is possible that very late relapses will occur in a few more patients, it remains exceptionally unlikely that all seven patients with positive results on both the PCR assay and the blast-colony assay and the seven other patients with positive PCR results alone will have relapses.

Experiments to determine the nature of the persistently positive cells, as Greaves suggests, are under way. We hope to determine whether these cells retain a malignant potential and, if so, to discern the mechanisms in the host that control their growth. Such a discovery may affect the treatment of future generations of children with ALL.

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