Residual leukaemia was not associated with relapse and was present during remission in children with acute lymphoblastic leukaemia

Roberts WM, Estrov Z, Ouspenskaia MV, et al. **Measurement of residual leukemia during remission in childhood acute lymphoblastic leukemia.** N Engl J Med. 1997 Jan 30; 336:317-23.

Objective
To determine whether submicroscopic evidence of residual leukaemia predicts the outcome of treatment in children with acute lymphoblastic leukaemia.

Design
Inception cohort evaluated over a 5-year period.

Setting
A cancer centre in the United States.

Patients
25 consecutive patients who were having a first clinical remission (defined as < 5% lymphoblasts in a cellular marrow specimen) after chemotherapy for B-precursor acute lymphoblastic leukaemia. Follow-up was 96%.

Assessment of prognostic factors
During remission, bone marrow aspirates were obtained at the end of therapy and every 3 months thereafter. Polymerase chain reaction (PCR) amplification of bone marrow DNA samples was done to determine the presence of residual leukaemia in all samples, and a limiting-dilution method of PCR was used to quantify the residual leukaemia in all but 12.5% of samples. Lymphoblast-colony assay was used to verify the presence of viable leukaemia cells.

Main outcome measures
Rate and site of clinical relapse and the presence of persistent leukaemia as determined by PCR and lymphoblast-colony assay.

Main results
24 patients were included in the analysis (1 patient was lost to follow-up). 15 patients were initially at standard risk, 7 patients were at intermediate risk, and 3 patients were at high risk for relapse according to previously established prognostic factors. 7 patients (29%) had a relapse (5 in the bone marrow [2 of these during therapy], 1 in the central nervous system, and 1 in both sites). Levels of residual leukaemia-cell DNA were higher in patients who relapsed than in those who remained in remission ($P < 0.001$). However, the estimated mean level of residual leukaemia-cell DNA was not associated with the probability of relapse. After completion of treatment, PCR detected residual leukaemia-cell DNA in 15 of the 17 (88%) patients who remained in remission and in all 5 who relapsed. Lympholast-colony assay results were available for 12 of the 15 patients with a positive PCR test and for 4 of the 5 patients who relapsed after completion of therapy. The assay was positive for all 4 patients who relapsed; in 7 of 12 remission patients with a positive PCR, at least 1 sample was positive. The assay was negative for both patients with negative PCR results.

Conclusion
Continued remission after chemotherapy may not require the elimination of all leukaemia cells in children with acute lymphoblastic leukaemia.

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Commentary

20% to 30% of children with acute lymphoblastic leukemia will die of their disease. Presently, it is common to modify the therapy of patients according to the risks identified at diagnosis. This inevitably leads to over- and under-treatment. It is hoped that a reliable technique for quantitation of residual leukaemia may help to optimise the duration and intensity of therapy. A review of 20 clinical trials found that most studies had a consistent pattern of residual leukaemia disappearance over several months in patients who remained in extended complete remission and that there was a pattern of residual disease persistence and reappearance preceding clinical relapse (1). However, other investigators have found drawbacks associated with the PCR detection of residual leukaemia, such as variability between laboratories, false-positive or false-negative results, and inconsistency of correlation with clinical outcome (2).

This small, prospective study by Roberts and colleagues suggests that most patients have detectable disease whether or not they are observed to remain in remission. It also suggests that the absolute level of residual leukaemia is not predictive of relapse but an increased level of residual leukaemia may be.

The high sensitivity of this test achieved a lower predictive value than hoped. However, it suggested that persistence of leukaemia detected by both PCR and lymphoblast-colony assay may be found in most patients thought to be in remission and possibly even cured. This raises the question of why some patients relapse, while others with the identical level of persistent disease do not. Only larger prospective studies can elucidate the utility of the measurement of residual disease and, ultimately, whether alterations of patient therapy based on these results will lead to improved clinical outcomes.

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