Flow-cytometric detection of minimal residual disease in adult acute lymphoblastic leukemia

The persistence of minimal residual disease (MRD) following the induction of complete remission (CR) in patients with acute lymphoblastic leukemia (ALL) predicts a poor outcome in childhood, whereas fewer data are so far available in adults.[1-6] In the present study we investigated MRD in a single center series of 24 adult patients with ALL using a flow-cytometric approach based on the detection of leukemia-specific marker combinations.[6-9]

From September 1994 to December 2000 we monitored minimal residual disease (MRD) in 24 adult patients with acute lymphoblastic leukemia (ALL) (11 T-, 13 B-lineage-ALL, representing 100% and 34% of observed cases, respectively). The investigated phenotypes were the co-expression of cytoplasmic CD3 (cyCD3) and nuclear terminal-deoxynucleotidyl-transferase (TdT) in T-ALL (observed in all cases), and myeloid marker (CD13/CD33) co-expression by $CD19^+/TdT^+$ cells in B-lineage-ALL (observed in 13/38 consecutive cases). $CyCD3+/TdT^+$ and $CD19^+/CD13^+/CD33^+/TdT^+$ cell clusters were expressed as absolute number and considered as MRD when consisting in more than 10 cells/100,000 acquired mononuclear cells (equivalent to a flow-cytometric sensitivity of 10^{-4}).[1–9]

Patients were treated with the ALL-VR95 protocol.[10] Two Philadelphia-chromosome positive (Ph+) B-lineage-ALL patients underwent autologous peripheral blood stem cell transplantation after induction. Seven high-risk patients (hyperleukocytosis, with hyperploidy in1 B-lineage-ALL case) underwent allogeneic bone marrow transplantation (BMT). The median follow-up was 36 months (range 6-61) for T-ALL and 19 months (range 3-51) for

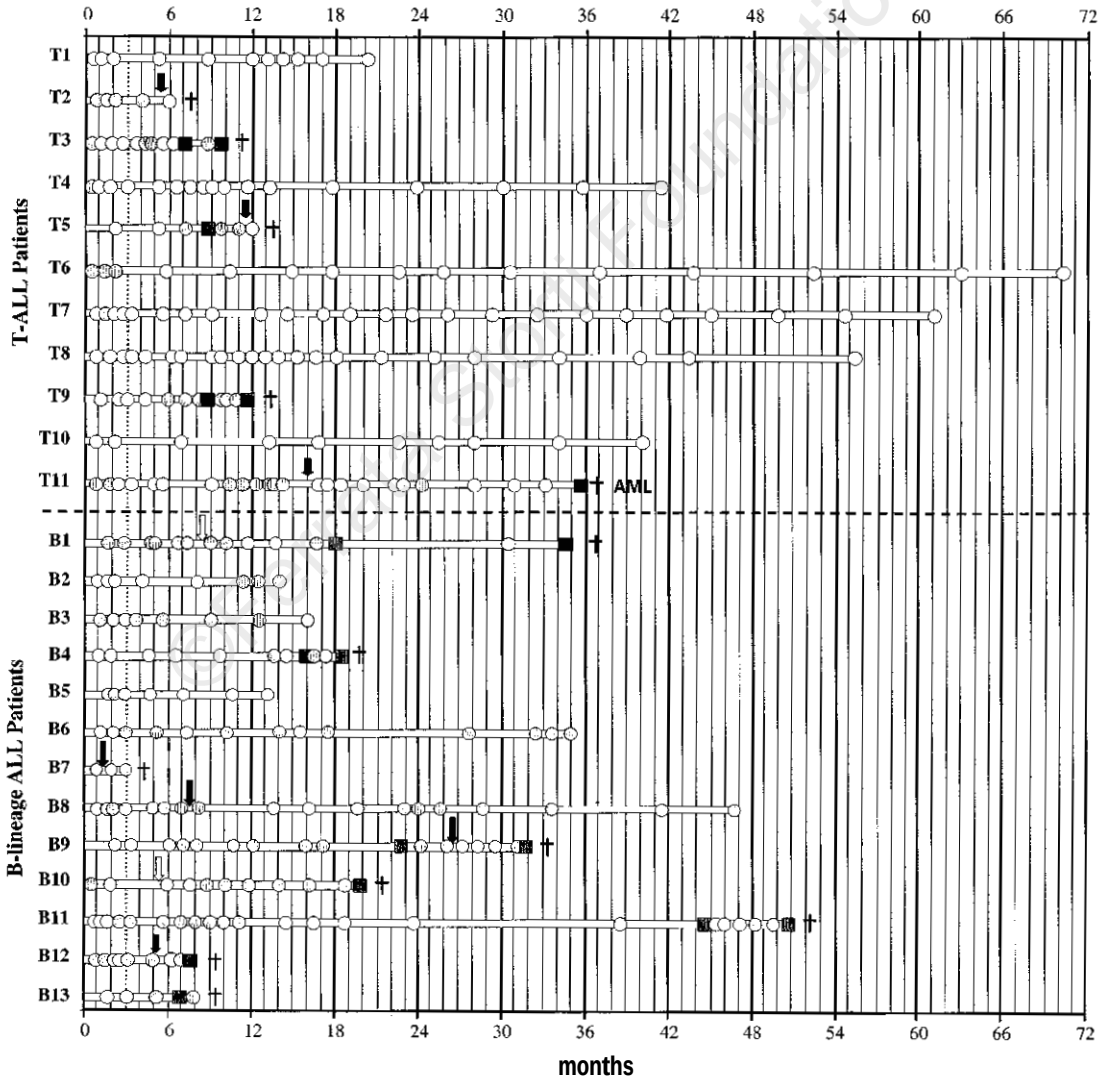

Figure 1. Flow-cytometric detection of minimal residual disease in adult T- and B-lineage-ALL patients.
○ complete remission (CR) / MRD⁻; ● CR / MRD⁺; ■ relapse; † = death; ⇀ allogeneic bone marrow transplantation (BMT); ⇁ autologous peripheral blood stem cell transplantation (PBSCT). AML: acute myeloid leukemia.

B-lineage ALL patients. Immunophenotypic MRD detection was performed on bone marrow samples on average 6 times/patient/year after diagnosis (first year: 8 times/patient/year for T-ALL and 6 for B-lineage-ALL, then 3 times/patient/year for all patients). We then correlated the current status of patients to MRD findings at 3 months (after induction /consolidation therapy and central nervous system prophylaxis), and 6 months after diagnosis (during reinduction cycles),[10] as previously suggested.[8] The results are shown in Figure 1. Ten of the 24 patients relapsed (3 T-ALL and 7 B-lineage ALL). MRD was detected prior to the relapse in all the T-ALL patients but one (T3, relapsed at +7 months, MRD negative in the last two controls). In the other 2 patients MRD was negative at +3 months, but positive at +6 months (T9, relapsed at +9 months) and +7 months (T5, relapsed at +9 months). All the B-lineage ALL patients were MRD$^+$ before relapse, 5 patients at +3 and +6 months (B1,B9,B11,B12,B13) and 2 later (B4, MRD$^+$ at +13/+14 months who then relapsed at +16 months after diagnosis; and B10, persistently MRD$^+$ from +7 to +19 months who then relapsed at +20 months after diagnosis).

Nine of the 24 patients are in continuous CR (CCR) with undetectable MRD: 8 of the patients with T-ALL (T1, T2, T4, T6, T7, T8, T10, T11; follow-up: 6-70 months; T11 died of acute myeloid leukemia after BMT) and 1 of the 13 patients with B-lineage ALL (B5, follow-up: 13 months). MRD was detected just at +3 months in 3 patients (T2, deceased at +6 months of BMT complications, T6 and B5).

Five of the 24 patients, all B-lineage ALL, are in CCR with detectable MRD. One (B7) died of BMT complications at +6 months; the others (B2, B3, B6, B8) are persistently MRD$^+$ (follow-up: 14, 16, 35 and 47 months, respectively). The immunophenotypic detection of MRD had a predictive value in 9/10 relapsed patients (90%), but not always were the controls at +3 and +6 months after diagnosis so informative. Undetectable MRD was clearly associated with CCR in T-ALL, whereas data were not so clear-cut in B-lineage ALL in which a longer follow-up might clarify the clinical outcome of CR/MRD$^+$ cases.

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