Determination of Residual Disease in Acute Leukemia by Flow Cytometry

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CONFERENCIA

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Studies of minimal residual disease (MRD), defined as leukemia undetectable by morphologic analysis, promise to improve the determination of initial treatment response and the clinical management of leukemia patients. The most reliable methods to study MRD are flow cytometric detection of aberrant immunophenotypes and polymerase chain reaction amplification of rearranged antigen receptor genes and chromosomal breakpoints. These methods can detect 1 leukemic cells among 10,000 or more normal bone marrow or peripheral blood cells. The results obtained with the two methods in childhood acute lymphoblasic leukemia (ALL) are highly concordant. Application of the two methods in tandem allows the monitoring of all patients. In patients with acute myeloid leukemia (AML), flow cytometry is the only method that allows MRD monitoring in the majority of patients. Prospective studies of MRD in children with newly diagnosed ALL and AML have shown that presence of MRD in bone marrow is strongly and independently associated with a higher risk of relapse. MRD studies are typically performed in bone marrow but we found that MRD findings in bone marrow and peripheral blood were highly concordant in paired samples from patients with T-lineage ALL, suggesting that in patients with this form of leukemia MRD could be monitored in blood. In addition to providing information that may directly improve treatment quality, MRD results can be used as endpoints for studies that aim at identifying predictors of drug resistance in vivo. Comparisons of genome-wide expression profiling at diagnosis and MRD during induction therapy allowed us to identify several genes (mostly involved in cell proliferation and apoptosis) that are strongly associated with MRD and predict treatment outcome. The mechanisms that lead to the persistence of MRD remain to be elucidated. Modern flow cytometers that allow the measurement of an increasing number of parameters offer unique opportunities to define the biologic features of the drug-resistant cells that constitute MRD, and determine whether these differ from the bulk leukemic cell population. The knowledge gained should aid the interpretation of MRD findings and might generate new hypotheses about ways to eradicate MRD and improve cure rates.