Detection and Elimination of Minimal Residual Disease in Patients with Acute Leukemia

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CONFERENCIA

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Studies of minimal residual disease (MRD) have become an important component in the clinical management of patients with acute leukemia. Prospective studies of MRD in children with newly diagnosed acute lymphoblastic leukemia (ALL) have shown that the presence of MRD in bone marrow is strongly and independently associated with a higher risk of relapse. Conversely, patients who are already MRD-negative after 2 weeks of initiation of treatment have an excellent treatment outcome. Therefore, MRD determinations are being used to select the intensity of therapy in childhood ALL protocols, with the aim of avoiding under- and overtreatment. Likewise, prospective studies in patients with acute myeloid leukemia (AML) have demonstrated the prognostic importance of these measurements in both children and adults, which are currently being applied for risk classification. We recently found that bone marrow mesenchymal cells protect ALL cells from L-asparaginase toxicity by providing a mileu rich in asparagine. These results, together with data from other laboratories, indicate that the bone marrow microenvironment creates a safe haven for leukemic cells. Therefore, agents that interfere with the interaction between leukemic cells and the microenvironment might enhance the effect of chemotherapy drugs. Finally, we developed a method to activate and expand natural killer (NK) cells and found that the cytotoxicity of these cells against AML cells is significantly more powerful than that exerted by primary NK cells. At the same time, we found that expanded NK cells expressing a chimeric receptor directed against CD19 exerted strong cytotoxicity against B-lineage ALL. Therefore, we have designed clinical protocols in which haploidentical NK cells expanded ex vivo will be infused in patients with drug-resistant leukemia. Ultimately, the improved accuracy of MRD-guided chemotherapy and the introduction of novel therapeutic agents able to bypass mechanisms of drug resistance should lead to an increase in cure rates and a decrease in treatment-related toxicities.