Human cytokine-induced memory-like NK cells expand in patients with AML and display enhanced anti-leukemia responses.

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Natural killer (NK) cells are an emerging cellular immunotherapy for patients with acute myeloid leukemia (AML); however, the best approach to maximize NK cell anti-leukemia potential is unclear. Cytokine-induced memory-like NK cells differentiate after a brief pre-activation with IL-12/15/18 and exhibit enhanced responses to cytokine or activating receptor re-stimulation for weeks to months after pre-activation. We hypothesized that memory-like NK cells exhibit enhanced anti-leukemia functionality. Because NK cell specificities depend on the multiple activating and inhibitory receptors, we developed mass cytometry panels to immunophenotype and track the diversity of these human memory-like NK cells in vitro and ex vivo. Using mass cytometry, we identified that memory-like NK cell functional responses were triggered against primary AML blasts regardless of KIR-ligand interactions. Multidimensional analyses identified distinct phenotypes of control and memory-like NK cells from the same individuals. In vitro differentiated memory-like NK cells did not display altered inhibitory KIR receptor repertoires when compared to baseline or control-treated cells (Inverse-Simpson Diversity Index), suggesting that cytokine pre-activation does not expand a specific KIR+ subset. In the context of a first-in-human phase 1 clinical trial, adoptively transferred memory-like NK cells proliferated and expanded in relapsed/refractory AML patients, and demonstrated robust responses against leukemia targets. Clinical responses were observed in five of nine evaluable patients, including four complete remissions. Mass cytometry revealed that in vivo-differentiated memory-like NK cells were distinct from baseline and pre-activated NK cells from the same donor. Deep immunophenotyping of in vivo differentiated memory-like NK cells in additional patients is ongoing, and has the potential to reveal complex immune signatures of transferred NK cells that contribute to the efficacy of this treatment modality. In conclusion, human cytokine-induced memory-like NK cells expand and have enhanced anti-AML function following adoptive transfer in patients, thereby constituting a promising innovation for the immunotherapy of AML.

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