CD4(+)and CD8(+)T-cell reactions against leukemia-associated- or minor-histocompatibility-antigens in AML-patients after allogeneic SCT.

Abstract:
T-cells play an important role in the remission-maintenance in AML-patients (pts) after SCT, however the role of LAA- (WT1, PR1, PRAME) or minor-histocompatibility (mHag, HA1) antigen-specific CD4(+) and CD8(+)T-cells is not defined. A LAA/HA1-peptide/protein stimulation, cloning and monitoring strategy for specific CD8(+)/CD4(+)T-cells in AML-pts after SCT is given. Our results show that (1) LAA-peptide-specific CD8+T-cells are detectable in every AML-pt after SCT. CD8(+)T-cells, recognizing two different antigens detectable in 5 of 7 cases correlate with long-lasting remissions. Clonal TCR-V?-restriction exemplarily proven by spectratyping in PRAME-specific CD8(+)T-cells; high PRAME-peptide-reactivity was CD4(+)-associated, as shown by IFN-?-release. (2) Two types of antigen-presenting cells (APCs) were tested for presentation of LAA/HA1-proteins to CD4(+)T-cells: miniEBV-transduced lymphoblastoid cells (B-cell-source) and CD4-depleted MNC (source for B-cell/monocyte/DC). We provide a refined cloning-system for proliferating, CD40L(+)/CD4(+)T-cells after LAA/HA1-stimulation.
CD4(+)T-cells produced cytokines (GM-CSF, IFN-?) upon exposure to LAA/HA1-stimulation until after at least 7 restimulations and demonstrated cytotoxic activity against naive blasts, but not fibroblasts. Antileukemic activity of unstimulated, stimulated or cloned CD4(+)T-cells correlated with defined T-cell-subtypes and the clinical course of the disease. In conclusion we provide immunological tools to enrich and monitor LAA/HA1-CD4(+) and CD8(+)T-cells in AML-pts after SCT and generate data with relevant prognostic value. We were able to demonstrate the presence of LAA-peptide-specific CD8(+)T-cell clones in AML-pts after SCT. In addition, we were also able to enrich specific antileukemic reactive CD4(+)T-cells without GvH-reactivity upon repeated LAA/HA1-protein stimulation and limiting dilution cloning.

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