

Next-generation dendritic cell vaccination as postremission therapy in AML

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Postremission therapy of patients with acute myeloid leukemia (AML) is critical for the elimination of minimal residual disease (MRD) and a prerequisite for achieving cure. Cellular immunotherapy is a highly effective treatment option as demonstrated by the low relapse rate after allogeneic stem cell transplantation (SCT). However, many patients are not eligible for this treatment. Therapeutic vaccination with autologous, antigen-loaded dendritic cells (DCs) is a promising strategy to induce cellular and humoral immune responses. Within recent years, we have developed a GMP-compliant protocol for the generation of *next-generation* DCs. A short, 3-day differentiation period is combined with a novel maturation cocktail that includes a TLR7/8 agonist. The resulting DCs are characterized by a positive costimulatory profile and a high production of bioactive IL-12p70. Both *in vitro* and *in vivo*, they have been shown to polarize CD4⁺ T cells into Th1, to induce antigen-specific CD8⁺ T cells and to activate NK cells.

We are currently conducting a proof-of-concept phase I/II clinical trial evaluating *next-generation* DCs as postremission therapy for AML patients with a non-favorable risk profile (NCT01734304). Standard exclusion criteria apply, and patients have to be ineligible for allogeneic SCT. DCs are generated from monocytes of the patients and then loaded with ivt-RNA encoding the leukemia-associated antigens WT1 and PRAME. Additionally, DCs trans-

duced with RNA encoding CMV-pp65 are included as an adjuvant and surrogate antigen. Patients are vaccinated intradermally with one batch of 5×10^6 DCs for each of the three antigens up to 10 times within 26 weeks. The primary endpoint of the trial is feasibility and safety. Secondary endpoints are immune responses and disease control, with particular focus on MRD conversion. Phase I will include 6 patients, and phase II another 14 patients. So far, two patients have been enrolled into the phase I of the trial. Pt. 1 was a 72 year-old man in CR with an adverse genetic risk profile (complex karyotype) and not eligible for allogeneic SCT. The differential blood count showed 11% monocytes of 7,6 G/l leukocytes (836 monocytes/ μ l). The leukapheresis yielded $3,4 \times 10^9$ monocytes in total, and 14 vials of DCs per antigen were generated for clinical application. Pt. 2 was a 54 year-old man in CRi with an intermediate genetic risk group (cytogenetic abnormality not classified as favorable or adverse) and no HLA-matched donor. The differential blood count showed 7% monocytes of 5,9 G/l leukocytes (413 monocytes/ μ l). The leukapheresis yielded $2,2 \times 10^9$ monocytes in total, and 6 vials of DCs per antigen were generated for clinical application. For both patients, the DCs fulfilled all quality criteria (cell count, viability, purity, sterility, phenotype). No adverse events have been observed so far except for slight erythema at the injection site. Up-to-date clinical and immunomonitoring data will be presented.