Immune monitoring of vaccine quality and persistence of specific T cell responses in five AML patients receiving extended dendritic cell vaccination under compassionate use

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Introduction

High dose chemotherapy and/or stem cell transplantation (SCT) are standard therapies with a potential curative effect for AML patients. Nevertheless, there is a high need to establish alternative treatment options for patients who are not eligible for standard treatment due to age or poor health.

We have treated five AML patients with no alternative treatment options under compassionate use with autologous TLR 7/8 polarized fast dendritic cell (DC) vaccines loaded with Wilms’ tumor-1 (WT-1) and preferentially expressed antigen in melanoma (PRAME) encoding mRNA with the intention to induce or support immune responses, thus preventing or delaying relapse.

Here we report immune monitoring results comprising the quality of the applied DCs as well as the specificity and persistence of T cell responses.

Vaccination Plan

Week 1 2 3 4 6 10 14 18

vaccine 1–4: monthly boost
DTH - Challenge
Dosage/injection: 2.5 – 5 x 10^6 DCs/antigen

Patients were given four vaccines in weekly intervals followed by monthly boosts. 2.5 – 5 x 10^6 DCs/antigen were injected intradermally at different sites.

Blood samples for immune monitoring were taken at baseline (BL), at time point of DTH challenge and monthly thereafter.

Patient Information

<table>
<thead>
<tr>
<th>Patient</th>
<th>CU030</th>
<th>CU031</th>
<th>CU033</th>
<th>CU040</th>
<th>CU041</th>
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<tr>
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<td>m</td>
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<td>Months of DC vaccination</td>
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<td>10</td>
<td>24</td>
<td>12</td>
<td>37 (continued)</td>
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<td>59 (drop out after heart failure)</td>
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</table>

Flow analysis: CU030 (representative for all productions)

IL-12p70 and IL-10 release upon CD40L stimulation of 20,000 DCs/well

Intracellular IFNγ staining:

ELISpot: CU030

Above: Intracellular IFNγ staining after stimulation with overlapping peptide pools.
CU031 lost WT-1 response after cortisone therapy.
Patients CU033 and CU041 showed initially only weak or no immune responses. Surprisingly, they could be visualized when adding anti PD-1 antibody to the culture.

Left: Control of immune response assessment by standard IFNγ ELISpot assay. Stimulation with overlapping peptide pools. Asterisks indicate significant results compared to unstimulated control (p < 0.05) (Example: CU030)

Summary and Perspectives

All DC productions showed a mature phenotype and released IL-12p70 upon CD40 stimulation with no or significantly lower IL-10.

All patients received DC vaccination over an extended period of time.

Three patients are still alive, two patients more than 5 years after diagnosis, one patient more than 4 years after diagnosis, all without signs of relapse.

Persisting specific T cell responses during treatment were found in 4 of 5 patients, in two patients they were obscured but could be detected by blocking of PD-1.

Encouraged by these promising results we have currently ongoing a clinical phase II study using the same protocol to further investigate the effect of extended DC vaccination on immune responses and prevention of relapse.