Intradermal vidincel Vaccination in Measurable Residual Disease-positive Acute Myeloid Leukemia patients results in Increased Antigen Presenting cells and T-cells at the Injection Site and local Immune-Cell Interactions

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INTRODUCTION

Vididencel is an allogeneic leukemia-derived cell vaccine being developed as maintenance treatment in AML patients. Intradermal injection using vididencel is known to induce a local skin reaction, with local antigen processing by skin dendritic cells. Dendritic cells can migrate from the skin to the draining lymph nodes, where they present antigens, inducing T-cell immune responses (Figure 1). It was previously shown that vididencel is able to induce an influx of immune cells in the skin using standard immunohistochemistry (van de Loosdrecht[1], 2018). In this phase 2 study (ADVANCE-II, Clintrials.gov: NCT03697707) vididencel was investigated as in AML patients in CR1 with positive measurable residual disease (MRD+) status. Induction of systemic immune responses has been shown to correlate with clinical benefit (ASH2024, van de Loosdrecht[3]). Skin biopsies were taken to investigate the local immune response.

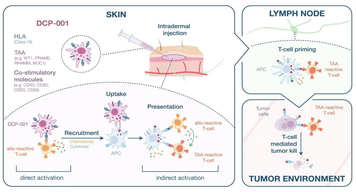


Figure 1. Mode of action vididencel (DCP-001)

DESIGN OF THE CLINICAL TRIAL

AML patients, in first complete remission with measurable residual disease (MRD$^+$) and not planned for HSCT at inclusion, received 4 bi-weekly doses of vididencel followed by 2 booster doses at week 14 and 18.

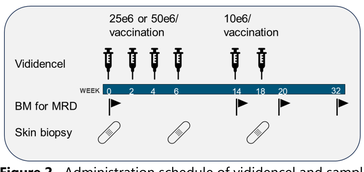


Figure 2. Administration schedule of vididencel and sampling frequency for bone marrow and skin biopsies.

MATERIALS & METHODS

Skin biopsies of the injection site were taken 2 days after the 1st, 4th and 6th vaccination.

Samples were fixed and embedded in paraffin in the central lab. In a subset of patients treated at Haukeland University Hospital (N=6), tissue sections were prepared, mounted and stained with the panel of 29 antibodies labelled with heavy metals for use in the "Hyperion™ Imaging System" utilizing imaging mass cytometer (IMC). For each sample a section of ~2.8 mm2 (between 1-4mm^2) was scanned, guided by standard H&E staining to the immune infiltrated parts.

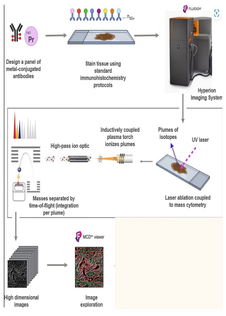


Figure 3. Short explanation of Hyperion mass cytometry for skin biopsy analyses. Image from 10.3389/fimmu.2022.859414[2]

RESULTS

In 88.5% of patients, injection site reactions were reported after injection of vididencel in the phase 2 study, characterized by redness, swelling and warmth at site of injection, which were mild (max. grade 1 or 2), and of short duration (generally resolved within 12 days). In normal H&E a large influx of immune cells was observed as compared to normal skin (Fig 3A and C).

Influx of CD4 and CD8 T-cells with or without memory marker CD45RA (Fig 3D) or activation markers like CD38 and Granzyme B expression (Fig 3E) was observed, suggestive for a diverse T-cell influx in the injected skin. Granzyme B expression was also observed in CD68 expression antigen presenting cells (Fig 3F). CD141+ and CD1c dendritic cells are observed close to vessels (Fig 3G), as well as in close contact with CD4 and CD8 T-cells, suggestive for patients' dendritic cells migrating from blood to skin, inducing a local immune response. CD141 staining not only stained the CD141+ DC, but also endothelial cells and skin keratinocytes, known to have CD141 expression as well.

Use of Imaging Mass Cytometry (IMC) with additional markers to characterize monocytes, dendritic cells, and T-cells unveiled their close proximity, suggesting a close T:DC cell interaction at site of injection.

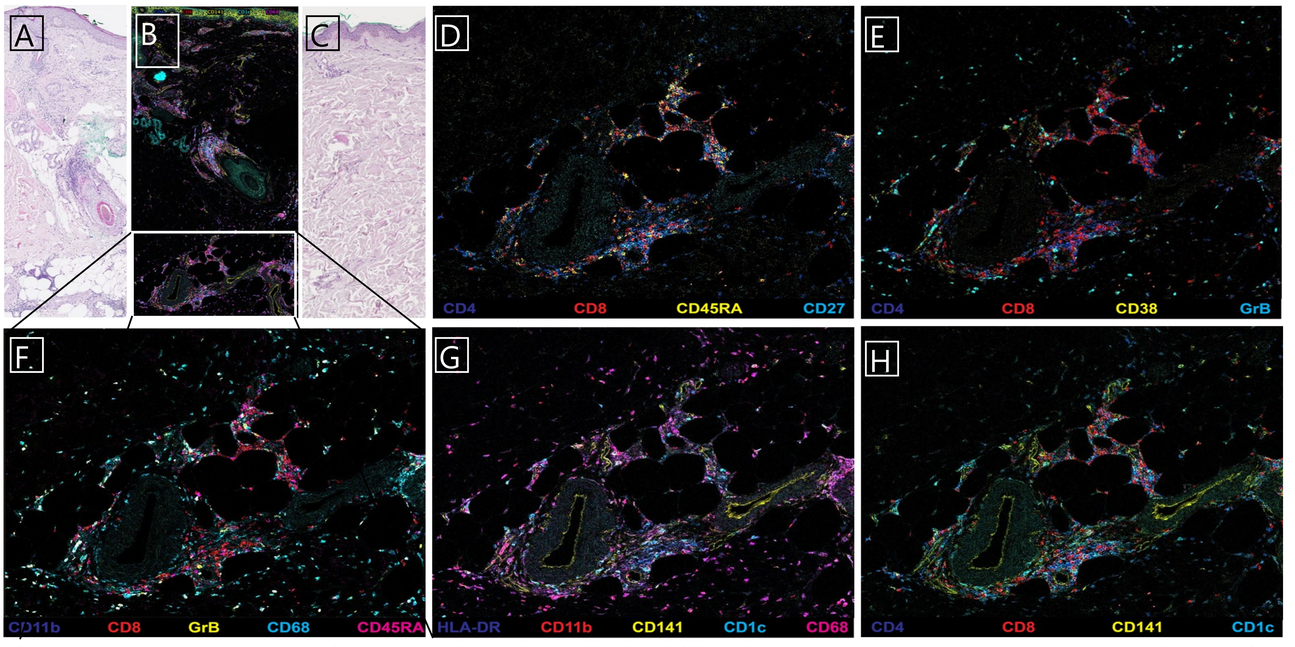


Figure 3. Representative staining of skin biopsy of patient 2 days after 4th injection of vididencel. **A** Overview H&E staining of the section. Note the influx of T-cells. **B**. Staining with CD4, CD8, CD68, CD1c and CD141; indicated is the close up. **C**. Representative H&E staining of a tissue section of patients normal skin (far from the injection site, were only few immune cells can be observed). **D.** Influx of CD4 and CD8 T-cells either or not expressing CD45RA (memory vs effector and naïve) and CD27. **E.** Expression of activation marker Granzyme B and CD38 in close connection to in particular CD8 and CD4 T-cells. **F.** Granzyme B expression by CD8 T-cells and CD68 macrophages. **G.** Areas with dense infiltration of dendritic cells, expressing high levels of HLA-DR and either CD1c or CD141, surrounded by CD68 expressing cells. CD141 is also expressed on endothelial cells and skin keratinocytes, as can be observed on the inner lining of the vessel (see arrow). **H** CD1c and CD141 dendritic cells and CD4 and CD8 T-cells indicates the close connection and immunological talk amongst these cells. Also note the dense efflux or infiltration close to vessels, indicating the recruitment of blood derived cells after injection of vididencel in conjunction with possible skin resident macrophages or dendritic cells.

CONCLUSIONS

Injection of vididencel causes a transient local skin reaction with redness, warmth and swelling.

CD4, CD8 T-cells and antigen presenting dendritic cells, with high expression of HLA-DR, CD141 and CD1c are recruited in high numbers in skin biopsies taken close to site of injection.

Close interactions are observed between all immune cells, especially T-cells and dendritic cells extravasating from blood vessels.

Support of hypothesis of local antigen capturing by blood derived and local antigen presenting cells.

Imaging mass cytometry combines regular and more rare antibodies in one slide analysis, providing deep insights in the local immune response following vididencel injection in the skin.

References 1.van de Loosdrecht AA et al., Cancer Immunol. Immunother. 2018; 67;1508-18. 2 Le Rochais et al., Application of High-Throughput Imaging Mass cytometry Hyperion in Cancer research 3. van de Loosdrecht et al., Blood 2014; 144: 2875