Early effects of venetoclax monotherapy on immune cells in patients with chronic lymphocytic leukemia

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by dysregulated apoptosis and impaired immune functions. Venetoclax is a selective small molecule that targets apoptosis via inhibition of B-cell lymphoma 2 (BCL-2). How venetoclax affects the immune system during early treatment has not been previously investigated.

In the current study, we analyse the immune cell profile in patients with CLL during early phases of treatment with venetoclax.

METHODS

Peripheral blood (PB) samples were collected from 10 patients with CLL at the Dept. of Hematology, Karolinska University Hospital, at baseline and at 4-6 hours (h), 24 h and 4 weeks after treatment start.

The starting dose was 20 mg, ramping up weekly to the final dose of 400 mg if tolerated. Six patients had relapsed refractory (R/R) disease and 4 patients were treatment-naïve. Eight healthy individuals were included as controls. PB cells were analysed by flow-cytometry. Plasma biomarker analysis by Olink is planned.

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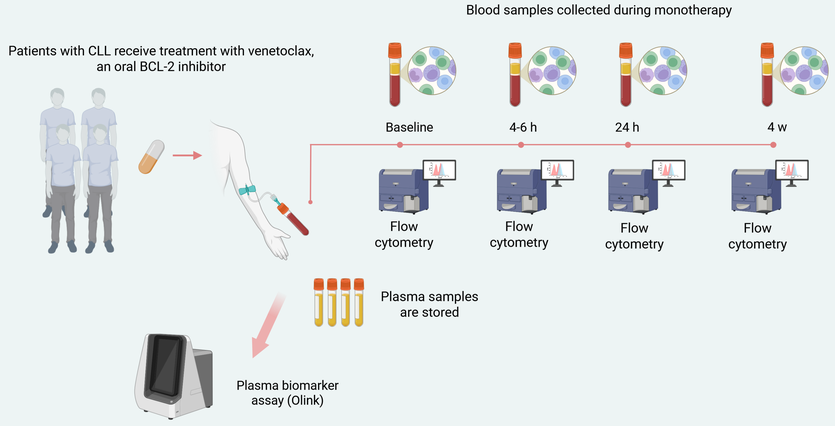

Figure 1. Study workflow for analysing early effects of venetoclax. Image created with Biorender.com.

RESULTS

At week 4, 7/10 patients had reached the full dose of 400 mg. The absolute number of CLL cells decreased significantly already at 4-6 h, and levels had normalized at week 4. Both $CD4^+$ and $CD8^+$ T cells decreased significantly at week 4 compared to baseline, with $CD4^+$ T cells being in the range of healthy controls at baseline and $CD8^+$ T cells were elevated.

Th1 cells showed a significant decrease at week 4, while Th2 cells did not change during treatment. Th17 and regulatory T cells (Tregs) decreased significantly at week 4. NK cells were within normal range at baseline and did not change throughout treatment.

The number of $CD4^+$ and $CD8^+$ cells co-expressing the exhaustion markers TIGIT and PD-1 were elevated at baseline, and both populations decreased significantly and normalized at week 4. A significant reduction was observed for most $CD4^+$ and $CD8^+$ T-cell memory populations at week 4.

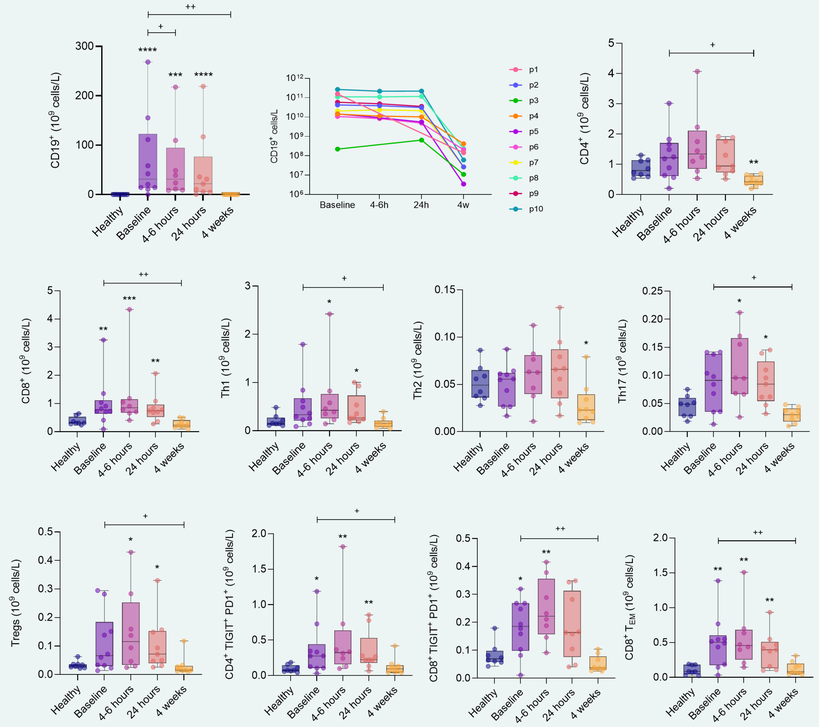

Figure 2. Immunological changes during treatment with venetoclax. **TIGIT**, T cell immunoreceptor with Ig and ITIM domains. **PD-1**, programmed cell death protein 1. Plus signs indicate a statistically significant difference between baseline and each respective time point as analyzed by Wilcoxon signed-rank tests. Stars indicate a statistically significant difference between healthy controls and each respective timepoint as analyzed by Mann-Whitney U-tests. +/* = p≤0.05, ++/** = p≤0.01, +++/*** = p≤0.001, ++++/**** = p≤0.0001.

CONCLUSIONS

We observed a significant decrease in CLL cells already at 4-6 h. After 4 weeks of treatment, several immune cells decreased including immunosuppressive features in T cells, possibly allowing for immune restoration following the reduction of leukemic cells.

Indirect effects might contribute to these changes, where depletion of CLL cells can eliminate the microenvironmental stimuli that recruit and support other immune cells.