Longitudinal analysis of the effect of the Btk inhibitor ibrutinib on the motility properties of CLL leukemic cells and T cells

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\textbf{Purpose:} Chronic Lymphocytic Leukemia (CLL) is a B-cell malignancy characterized by the accumulation of mature B cells in the blood and lymphoid organs, where they get access to proliferation niches. Btk is a central signaling molecule that integrates multiple environmental triggers in CLL cells. Recently, the first-in-class Btk inhibitor Ibrutinib has yielded outstanding efficacy in CLL patient treatment. Although Ibrutinib has been shown to reduce the chemokine-driven motility of CLL cells, the persistence of its effects on CLL cell motility along treatment remains to be explored. It also key to investigate whether Ibrutinib may affect the motility properties of CLL partner cells such as T lymphocytes.

\textbf{Experimental Design:} As part of the CompuTreatCLL interdisciplinary project, we are assessing the expression of phenotypic markers accounting for motility and adhesion, and the chemokine-driven migration of cells from patients at regular intervals following initiation of ibrutinib monotherapy.

\textbf{Results:} Our data indicate a decrease in leukemia cell migration in response to CCL19 and CXCL13 for all tested patients within the first 2 months of treatment. The migratory capacity of T cells was also affected with gradual decrease of migration to CCL19 and CXCL12 and more pronounced loss of migration to CXCL13 during the first 6 months of treatment. Parallel in vitro experiments revealed that ibrutinib affects, in CLL cells and T cells, both basal migration and cell orientation along chemokine gradients. The level of expression of the chemokine receptors specific of the tested chemokines (CCR7, CXCR4, CXCR5) decreased upon treatment at the surface of both CLL leukemic cells and T cells, therefore mirroring the impact of treatment on chemokine-driven motility. Additional phenotypic markers including chemokine receptors, adhesion molecules and activation markers are being evaluated in parallel.

\textbf{Conclusion:} The expression analysis of each marker, as well as the combination of several markers will be integrated into a model of dynamic redistribution of leukemic cells. This study should not only help to stratify patients, but also to extract predictive parameters of different patterns of disease progression under treatment.