Computational Integration to Model Tumor Dynamics in CLL Patients Treated with the Btk Inhibitor Ibrutinib (CompuTreatCLL): First Results of an Integrative Systems Biology Approach

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Purpose: Ibrutinib, Btk inhibitor, impairs BCR signaling, survival, and homing of leukemic cells, leading to the purge of CLL cells out of the lymphoid organs and/or induction of apoptosis. However, important inter-patient variability in the redistribution of the leukemic cells, the rate of their elimination and the disparity of relapses call for a systemic analysis of the parameters influencing the dynamical behavior of the leukemic cell population in individual patients. The global objective is to elaborate a computational model that accounts for the physical and biological evolution of the CLL leukemic cell population during ibrutinib therapy.

Experimental Design: Collected data stem from pharmacokinetic study, dynamic imaging (whole-body diffusion-weighted MRI+Tepscan day 0-1-12-24 months), clinical evolution, and in vitro read-outs of leukemic cell viability, tumoral heterogeneity and migrative/adhesion capacities of both tumoral B cells, and normal T cells.

Results: As described¹² in the first month of ibrutinib therapy we found that our first 27 patients segregate into 3 groups based on baseline fold-change of CD5⁺/CD19⁺ lymphocytes counts, monthly monitored from month 0-6 (n=9 each): group 1 had a transient lymphocytosis (<2mo); group 2 had reduction with no observable lymphocytosis; group 3 had a prolonged hyperlymphocytosis (>6mo). For the first time, we were able to correlate BTK/p-BTK levels, nodal/spleen bulk (cm³), absolute numbers of normal immune subsets, PK parameters and in vitro apoptotic response (0.25µM ibrutinib) measured at day 0 and day 30, to these 3 groups reflecting inter-patient variability.

At baseline, neither BTK/pBTK nor CD4/CD8/NK/B cells levels predict response at 1 month, but interestingly group 2 had significantly more Tregs cells and CD4/PD-1⁺ cells than groups 1 and 3. In vitro response to ibrutinib (0.25µM) was highly correlated to response group. Interestingly tissular disease (assessed with MRI) was not different among the 3 groups.

After one month, no PK parameter was correlated to response group. Median lymph node sizes reduction (evaluated with a in-house informatic delineation tool) tends to be significantly higher in groups 1 and 3 than in group 2.

Conclusion: The project is expected to identify biological parameters linked to the in vivo redistribution and clinical outcomes under ibrutinib treatment. Ultimately, a mathematical model based on the most relevant parameters will be elaborated with the perspective in the future to benchmark tumor microenvironment-targeting agents, and also maybe link cellularity to sub-clonal evolution.

References: