Mathematical model of the dynamics of lymphocyte cell counts of CLL patients under ibrutinib treatment

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Abstract

We propose two talks on the treatment of chronic lymphocytic leukemia (CLL) by Btk Inhibitor Ibrutinib. First, Anne Quillet-Mary will present the disease context as well as the analyses performed on a collection of data from patients included in a registered observational study (CompuTreatCLL). Second, Chloe Audebert will present a mathematical model of the dynamics of lymphocyte cell counts of CLL patients under ibrutinib treatment accounting for cell heterogeneity.

Chronic lymphocytic leukemia is the second most frequent form of lymphomas (5th cause of cancer in men, 7th cause of cancer in women, approximatively 4500 incident cases each year in France). The complexity of this hematological disease is reflected by its multiple localization generating different properties of leukemic B cells. Indeed, micro-environment plays a crucial role in lymphoid organs by maintaining survival and proliferation of leukemic B cells. In addition, blood circulating leukemic B cells are quiescent and resistant to spontaneous cell death (apoptosis). The treatment of this disease has been recently revolutionized by the replacement of immune-chemotherapies by targeted therapies. The Btk inhibitor ibrutinib has recently been approved as a monotherapy in relapsed/refractory CLL. It impairs B-cell receptor signalling, survival, and homing of leukemic cells, it purges these cells from the lymphoid organs and induces cell death. However, important inter-patient variability in the

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redistribution of the leukemic cells, the rate of leukemic cell elimination and the disparity of relapses calls for an analysis of biological parameters influencing the dynamical behavior of the leukemic cell population in individual patients.

The overall objective was to elaborate a computational model that accounts for the physical and biological evolution of the CLL leukemic cell population during ibrutinib therapy, to predict, at the start of the treatment, the clinical outcome and adapt the treatment. Through an interdisciplinary consortium, we collected and analysed data from patients included in a registered observational study. These data include dynamic imaging, clinical evolution, biological analyses. At the start of the treatment, we have defined biological parameters that correlate with clinical evolution of ibrutinib-treated patients. From these analyses we were able to establish two groups of patients with either poor or good response to the treatment. Some of the biological parameters found in the study were used to establish a mathematical model.

The dynamics of lymphocytes in patients treated with ibrutinib is very heterogeneous. In this second presentation, we will describe with ordinary differential equations leukemic and normal lymphocytes dynamics in CLL patients treated with ibrutinib. We want to account for inter-patient variability in cell count dynamics. To do so parameter estimation was performed with non-linear mixed effect models. The idea was to characterize the average behavior and to extract the individual dynamics from this behavior. In order to validate the methodology, we present results on synthetic data (data generated with the model). Finally, estimations were performed on real biological data from CompuTreatCLL cohort. We aim at discriminating the different responses to treatment based on parameters of the mathematical model.