Mathematical modeling of imatinib treatment in patients suffering from chronic myeloid leukemia

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Abstract Chronic myeloid leukemia (CML) is a clonal disorder of the hematopoietic system which results in an overproduction of (immature) myeloid blood cells. It is characterized by a long latency time, a period of coexistence of malignant and normal cells (chronic phase), and an eventual overgrowth of the system by the malignant clone. One promising therapeutic approach is the application of the tyrosine kinase inhibitor imatinib which is selectively acting on cancer cells. To better understand possible mechanisms of treatment evolvement and therapy effects, we applied a mathematical model of hematopoietic stem cell organization to the situation of CML. The model is based on a general concept of tissue stem cell organization, which explains the self-renewing capacity of primitive hematopoietic progenitors as a consequence of reversible, environment-dependent changes of actual expressed cell properties. The balanced supply of hematopoietic cells is achieved by the dynamic regulation of cell stroma attachment/detachment kinetics. We demonstrate that the model is able to explain the typical behavior of a growing malignant clone starting from the mutation of a single cell while being fully consistent with the above mentioned CML specific characteristics. Based on the interpretation of CML as a clonal competition of normal and malignant cells, we analyzed the effect of imatinib treatment. We show that our model is able to qualitatively explain clinically observed dynamics as well as inter-patient heterogeneity. Furthermore, we make quantitative predictions on the effect of cell cycle activity stimulating drugs additional to imatinib.