Mathematical Modeling of Clonal Selection and Therapy Resistance in Acute Leukemias

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Leukemia is a disease of the blood forming system leading to extensive expansion of malignant cells. Similar as the blood system, leukemias are maintained by a small population of leukemic stem cells that resist treatment and trigger relapse. Recent experimental evidence suggests that acute myeloid leukemias may originate from multiple clones of malignant cells. Nevertheless it is not known how the observed clones may differ with respect to cell properties such as proliferation and self-renewal. There are scarcely any data on how these cell properties change due to chemotherapy and relapse. We propose a new mathematical model to investigate the impact of cell properties on multi-clonal composition of leukemias. Considering a continuum of leukemic clones leads to a structured population model consisting of integro-differential equations with a nonlinear and nonlocal coupling. We show that such coupling leads to mass concentration in points corresponding to maximum of the self-renewal potential and the model solutions tend asymptotically to a linear combination of Dirac measures. Model results imply that enhanced self-renewal may be a key mechanism in the clonal selection process. Simulations suggest that fast proliferating and highly self-renewing cells dominate at primary diagnosis while relapse following therapy-induced remission is triggered mostly by highly self-renewing but slowly proliferating cells. Comparison of simulation results to patient data demonstrates that the proposed model is consistent with clinically observeddynamics based on a clonal selection process. Model based interpretation of clinical data allows to assess parameters that cannot be measured directly. This might have clinical implications for future treatment and follow-up strategies.

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