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Evolution of Clonal Heterogeneity in Chronic Myelomonocytic Leukemia

Chronic myelomonocytic leukemia (CMML) is an aggressive clonal hematopoietic malignancy hallmarked with monocytosis, cytopenia, and marrow dysplasia. CMML is poorly understood and has an overall unfavorable prognosis with a median survival of 34 months, and a 20-30% chance of progressing to acute myeloid leukemia with or without treatment. Currently, the only curative treatment option is an allogeneic stem cell transplantation, which many patients are not eligible for due to co-morbidities and advanced age. There is significant heterogeneity among patients, suggesting that there are several different evolutionary trajectories that shape disease formation and progression. In addition, here is still no codified way of uniformly stratifying risk groups and evaluating therapeutic tools. Recent findings indicate that inflammatory cytokines are over-expressed in chronic myeloid neoplasms and that these cytokines may contribute to leukemic initiation and proliferation. Most non-curative treatments revolve around cytoreductive chemo-therapies, which have limited activity and can facilitate selection of minor aggressive subclones. To better understand the evolutionary dynamics of heterogeneous CMML, we have developed a mathematical model. We study clonal evolution on the levels of inflammatory cytokines and their receptors, expressed on leukemia cells in the bone marrow microenvironment. Our modeling is based on individual patients' cytokine and cytokine receptor expression profiles. We compared healthy controls with CMML patients to establish a baseline model, and followed CMML patients over time. Each cytokine's inflammatory and proliferative potentials were used to inform the evo-lutionary dynamics. Our framework distinguishes between different regimes of clonal and overall tumor fitness to categorize and predict individual patient trajectories. Using this model, we seek to inform personalized treatment strategies that block inflammatory cytokine receptors in order to delay or prevent disease progression.