Stochastic modeling of imatinib-treated leukemic cell dynamics.

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Chronic Myeloid Leukemia (CML) is a slowly progressing cancer that makes the body produce too many cancerous myeloid white blood cells. The molecular characteristics of CML is the presence of the Philadelphia (Ph) chromosome, created by the reciprocal translocation of the ABL gene on chromosome 9 with the BCR gene on chromosome 22. The fused oncogene BCR-ABL influences the activity of large protein complexes that regulate the blood cell growth, producing an increasing number of immature white cells. All transforming activities of BCR-ABL mutant depend on its elevated tyrosine kinase activity. The introduction of the ABL tyrosine kinase inhibitor imatinib (Gleevec) for the treatment of CML represents the first example of a successful targeted therapy. Despite its striking efficacy, however, the development of resistance to imatinib is observed in a proportion of patients, especially those with advanced-stage CML.

Numerous studies on cancer genetics have confirmed the basic idea that cancer arises when a single cell experiences multiple mutations, inactivating the tumor suppressor genes (TSGs) in both alleles [1,2,3]. In the present work, the dynamics of the cancer progression is studied by modeling the stochastic evolution of a finite population of replicating cells. In our model, we consider three types of cells, denoted by 0, 1 and 2, because they contain 0, 1, and 2 mutations, respectively. Healthy cells (type 0) can experience a genetic mutation and transform to first-mutant cells (type 1). This population represents an intermediate phenotype, in which the first allele of the TSGs has been inactivated. A second genetic alteration is simulated to confer the malignant form to the cell and to generate cancerous clones (type 2). The evolutionary dynamics of this system of cells is described by a Moran process [4], in which cells reproduce asynchronously and each elementary step of the stochastic process consists of a birth and a death event. In this framework, mutations cause an increase of the net reproductive rate, providing a selective advantage for mutated cells.

Several scenarios of the evolutionary dynamics of imatinib-treated leukemic cells are described as a consequence of the efficacy of the different modeled therapies. Under specific conditions, an intrinsic periodicity of the evolutionary dynamics of malignant cells has been observed. The development of resistance is also investigated, as an induced effect of enhancement of the mutation rates caused by the therapy itself.