Fluctuations on cancer growth dynamics in Chronic Myeloid Leukemia

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I. INTRODUCTION

Chronic Myeloid Leukemia (CML) is a cancer of blood where too many myeloid cells (one of the main types of white blood cells) are produced and released into the blood when they are immature and unable to work properly. Despite the front line therapy for the treatment of CML, based on the administration of highly effective tyrosine kinase inhibitors (TKI), represents the first example of a successful molecular targeted therapy, the appearance of resistance is observed in a proportion of patients. The evolutionary dynamics of cancer initiation and progression can be theoretically approached by mathematical deterministic equations [1,2] or stochastic models[3–6], both using the basic idea that cancer arises when a single non-differentiated cell experiences multiple mutations.

In this work, we study the fluctuations on cancer growth dynamics in patients affected by CML and developing resistance to the standard therapy. The evolutionary dynamics of cancerous cell populations is modeled in numerically simulated patients treated by an intermittent targeted therapy (IT). In our model, initially healthy cells can experience genetic mutations and change their reproductive behavior, becoming leukemic clones. We simulate a TKIs-based treatment of CML by modifying the fitness and the death rate of cancerous cells. In CML context, a temporary interruption of the therapy was found to significantly reduce the presence of leukemic cells in a resistant patient[7,8]. Here we explore the fluctuations occurring in patient leukemic cells treated by a therapy where the simulated drug administration follows a continuous or pulsed time scheduling. A permanent disappearance of leukemic non-resistant clones is achieved with a continuous therapy. However, our findings demonstrate that an intermittent therapy could represent a valid alternative in patients with high risk of toxicity, being a suitably tuned pulsed therapy more effective to reduce the probability of developing resistance.

II. THE MODEL

In our model cells are distributed over four populations: healthy cells (type-0), first-mutated cells (type-1), double-mutated leukemic cells (type-2) and resistant leukemic clones (type-3). Each population is assumed to be composed of the sum of stem cells, progenitors, differentiated and terminally differentiated cells. We study the dynamics of N= 10^4 replicating cells. This value is several orders of magnitude lower than the typical total contents of blood cells in humans, but it is great enough for the statistical study of the cancer development in a single blood compartment. In order to simulate the random process of cell selection for reproduction, mutation and death we adopt a Monte Carlo approach, as already done in several theoretical studies[4–6]. Each elementary step of the stochastic process consists of a birth and a death event, i. e. a Moran process[9]. For the birth, one of the N cells is randomly chosen proportionally to its capacity to reproduce. The fitness of type-0 and type-1 cells are set equal to 1 as already adopted in other theoretical studies[4,6]. In the absence of therapy, the reproductive rate of a leukemic cell is assumed to be 10 times that of a normal cell. The treatment lowers this value only for those cells which are sensitive to the drug. The reproductive capability of resistant cells remains unchanged. Fitness values have been chosen in order to match the response of type-2 leukemic cells to that experimentally observed in patients treated by TKIs-based targeted therapy[1,3].

Healthy cells mutate to cells of type-1 (first allele mutation) at a rate M_{01} equal to 0.0005; type-1 cells mutate to type-2, which are leukemic cells sensitive to the therapy, at a rate M_{12} equal to 0.002. These values, comparable with the mutation rates adopted in the models of Refs.[1,4], guarantee a good agreement between our findings and clinical results. For the same reason, in our model we have assumed that type-2 cells become resistant type-3 by mutating at a rate M_{23} which has not a constant value, but increases with the number N_2 of leukemic double-mutated cells. The specific set of chromosomal mutations that causes the cancerous cell to become resistant can be considered an evolutionary reaction of the cell against the drug. On this basis we assume that, during the periods of absence of therapy, the mutation rate M_{23} is reduced to such very low values that we reasonably keep it equal to zero. In our simulations time is measured in units of cell divisions, and we assume 500 cell divisions per day. Using this time scaling from cell divisions to days we get a complete restore of healthy cells in almost 100 days, as experimentally observed in clinical cases of optimal therapy response[1,3].

III. NUMERICAL RESULTS AND DISCUSSION

Our simulated patients, subjected to a continuous therapy for the first 100 days, are then treated by three different therapeutic strategies characterized by: (i) continuous drug administration (namely, "CT"), (ii) long

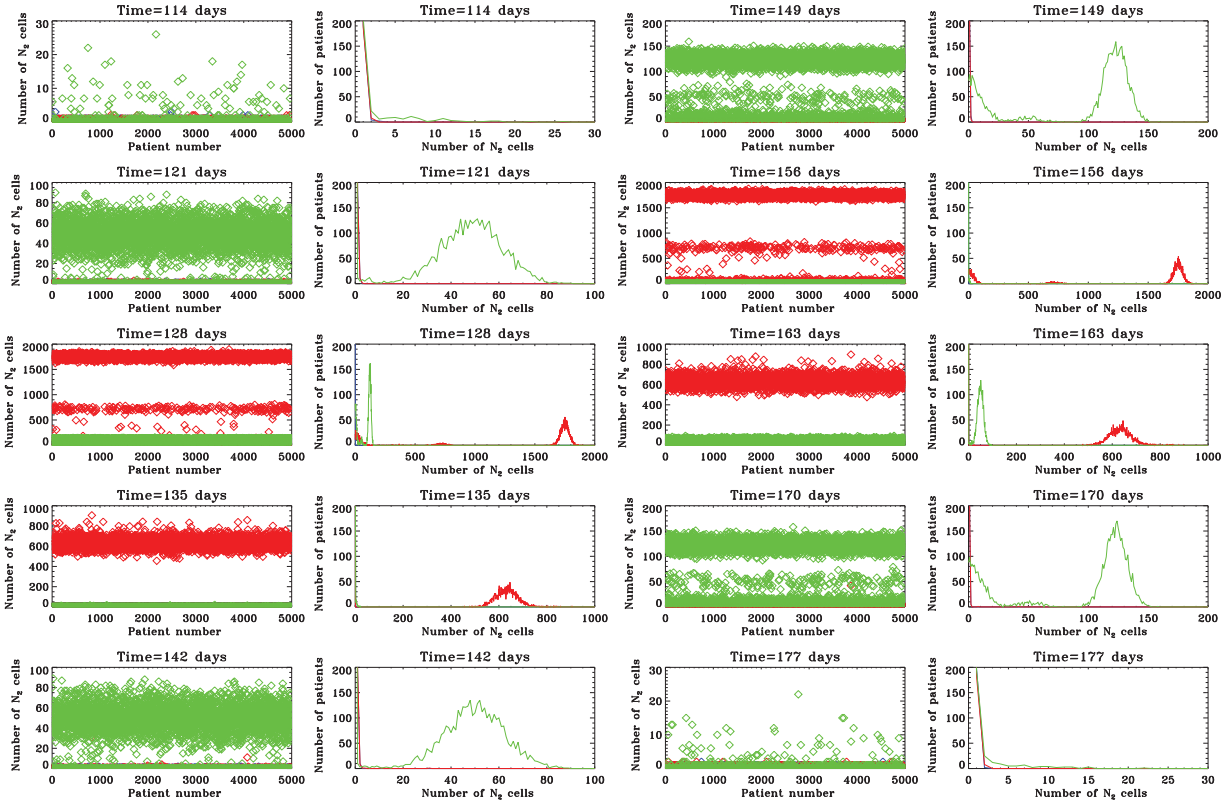

FIG. 1. Distributions of type-2 leukemic cells among patients. Blue symbols/curves refer to patients treated by a continuous therapy. Red and green diamonds/curves are used for intermittent therapies with breaks of 7 days and 1 day, respectively.

interruptions (7 days of stop after 21 of continuous therapy, namely "IT21-7") or (iii) short breaks (one day yes, one day no, namely "IT1"). In Fig. 1 we show how the number of type-2 leukemic cells is distributed among all the simulated patients after the first 100 days, at fixed time steps of 7 days for 10 weeks. In particular the blue colour is used for patients treated by CT, red for IT21-7 and green for IT1. Fig. 1 also shows the distribution of patients with a given number of type-2 leukemic cells. The crucial point for patient long-term survival to CML is avoiding those mutations causing a type-2 leukemic cell to become type-3 resistant to the therapy. In our model the occurrence probability for such harmful mutations depends on the presence of the drug, and increases with the number of type-2 leukemic cells. This is the reason why the study of fluctuations in the number of type-2 leukemic cells is so crucial for a clear estimate of the balance between the benefits of the therapy and the risk of developing cancer resistance. Of course the best results, in terms of lower levels of the type-2 leukemic cells, are achieved with a continuous therapy. However, the results shown in Fig. 1 demonstrate that an IT could also represent a valid choice in patients who cannot assume drug continuously due, for example, to a problem of toxicity. In fact, even if an increase of the average number of type-2 leukemic cells is observed during an intermittent therapy, this effect is partially counterbalanced by a reduction in the probability of developing resistance. Finally, our IT results clearly show the presence of multiple states of dynamical equilibrium in the number of type-2 leukemic cells. But, unfortunately, the most populated equilibrium state has always the highest number of leukemic cells. The possibility of achieving a population reverse in CML progression is still an unsolved problem.

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