A Personalized Framework for Dynamic Modelling of Chronic Lymphocytic Leukemia Disease Trajectories

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In the UK (Cancer Research UK, 2008), B-cell Chronic Lymphocytic Leukemia (CLL) is the most common form of leukaemia with 2,800 people diagnosed annually; 75% of these patients are older than 60 years of age. CLL is a heterogeneous leukemia with associated chromosomal mutations including del(13q14.1), del(11q), del(6q) and del(17p). Unlike Acute Leukemia, which typically involves uncontrolled growth of immature blood cells, CLL is usually a slowly progressive malignancy of mature B-cells that couples abnormal growth with resistance to apoptosis (programmed cell death).

Depending on disease progression and severity, CLL is categorized into 3 stages, known as Binet Stages (Binet, et al., 1981; Montserrat, et al., 1986). In the earliest stage, Stage A, CLL progression is slow with increased number of lymphocytes in peripheral blood (>5000 cells/μL) and fewer than three areas of enlarged lymph nodes; the CLL clone doubling time is approximately 70 months (>12 months) in peripheral blood. In the middle stage, Stage B, the number (and total area) of enlarged lymph nodes increase in the absence of anemia (low hemoglobin) and thrombocytopenia (low platelets) and the lymphocyte doubling time in peripheral blood decreases to 11 months (≤12 months) and remains almost stable. In the late stage, Stage C, the main findings are of anemia and/or thrombocytopenia, regardless of the number of areas of lymphoid enlargement; bone marrow failure is typical.

There is an unmet need to simulate the disease trajectory of cancers, such as CLL, in the human body; such models may improve clinical pathways for cancer treatment and enable personalized healthcare. This work proposes the first dynamic mathematical model of CLL that interconnects the most affected tissues: peripheral blood, lymph nodes, spleen and bone marrow. Prior to this work, Nanda et al. (2013) presented a mathematical model of CLL; the authors used a dynamic system of a single compartment to model the number of lymphocytes in untreated and treated patients with Binet Stage A CLL. In contrast, our model proposes to mathematically interconnect tumor-involved disease centers via cell migration. We show how our approach of considering both disease loci individually and in connection to one another can describe cancerous cell proliferation and the resultant disease sequela due to tumor cell accumulation in these tissues. Our model maps disease characteristics such as bone marrow infiltration, number of lymphocytes in peripheral blood and areas of enlarged lymph nodes to a systems engineering analysis. The springboard for this work is the Pefani et al. (2013; 2014) approach to modelling Acute Myeloid

Leukemia (AML). AML is a different disease, but we adapt from Pefani et al. (2013; 2014) the approach of concentrating on the relevant cell cycle characteristics in different tumor-involved tissues of the body.

Simulation results are presented using the derived model for multiple hypothetical patients based on published reports. The studied patients have different disease characteristics such as bone marrow infiltration pattern, enlarged lymph nodes and spleen sizes, number of lymphocytes and lymphocyte doubling time in peripheral blood. Each patient stage is different and disease progression from the one stage to the next is shown until the end-point of bone marrow failure occurs. All hypothetical patient studies are restricted to physiologically plausible state variable values; for example, CLL cells are restricted to proliferating at physiologically-relevant levels and capped at cell numbers relevant to the three-dimensional microenvironment of the bone marrow and lymph nodes. Moreover, the size and number of enlarged lymph nodes and dimensions of the enlarged spleen are predicted in each stage of the model.

Model analysis of these patient case studies reveals the potential progression of CLL in different patient types. We show how the proposed CLL modelling framework captures disease pathophysiology; understanding disease trajectories is critical for personalized medicine and is required for clinicians, experimentalists, and modellers to collaborate in treating cancers, especially in tumors such as CLL which has defined disease stages over years and provides opportunities for targeted intervention. Towards this end, mathematical modelling is undoubtedly useful in order to capture leukemia dynamics in humans and subsequently may provide insight into the causes and subsequent prevention or personalized treatment of disease progression. This effort belongs to the Biological Systems Engineering Laboratory and the Centre for Process Systems Engineering at Imperial College, where building blocks of a design framework for modeling and optimization of biomedical systems are developed (Velliou et al. 2014).

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