Managing Chemotherapy-Induced Neutropenia using Exogenous Granulocyte Colony-Stimulating Factor

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"Neutropenia" is a lethal condition of having a low number of neutrophils in blood circulation, leaving the body critically vulnerable against any kind of infection or disease. Neutropenia caused by chemotherapeutic damage on progenitor blood cells is called "Chemotherapy Induced Neutropenia" (CIN). Chemotherapy-induced neutropenia frequently threatens the continuity and effectiveness of chemotherapy since a heavily cytotoxic treatment such as chemotherapy can not be conducted on a patient with a vulnerable immune system (Crawford et al., 2004).

Exogenous administration of Granulocyte Colony-Stimulating Factor (G-CSF), a stimulating factor on neutrophil production, is used for the treatment of CIN to compensate for the destructive effect of chemotherapy by restoring neutrophil levels in blood circulation (Scott et al., 2003). However, constructing an effective treatment regime of CIN using G-CSF is a challenging task because of the feedback-rich and high order delayed structure of the system.

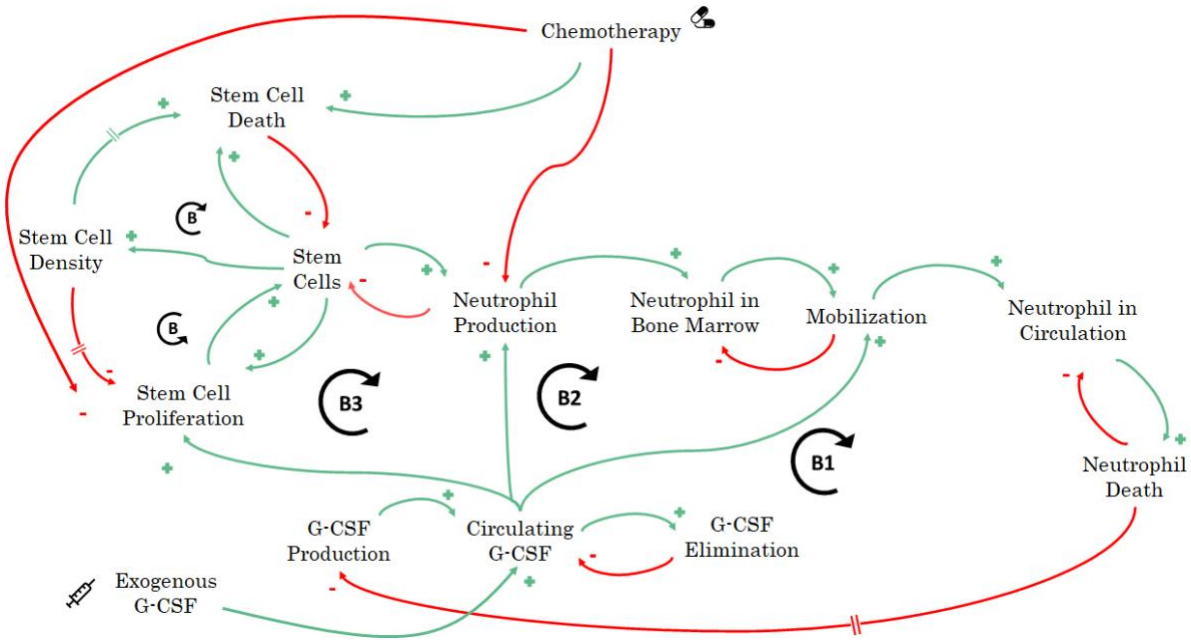

Figure 1: Simplified Causal Loop Diagram

In this study, a model that captures the behaviour of the blood dynamics under chemotherapy and G-CSF administration is built to analyze the dynamics of this physiological system. In this manner, internal neutrophil production, the chemotherapeutic effect on blood cells, and G-CSF's influence on blood cell stimulation are modeled as three interacting physiological processes. A simplified representation of these processes is provided in Figure 1.

Extensive literature research provided most of the parameters and the rest were calibrated under homeostatic conditions. The model is validated using real-life data from previous studies (Krzyzanski et al., 2010; Sholz et al., 2012). Absolute neutrophil count (ANC) response of the proposed model for one shot and seven consecutive daily G-CSF injections can be seen in Figure 2 along with the real-life data.

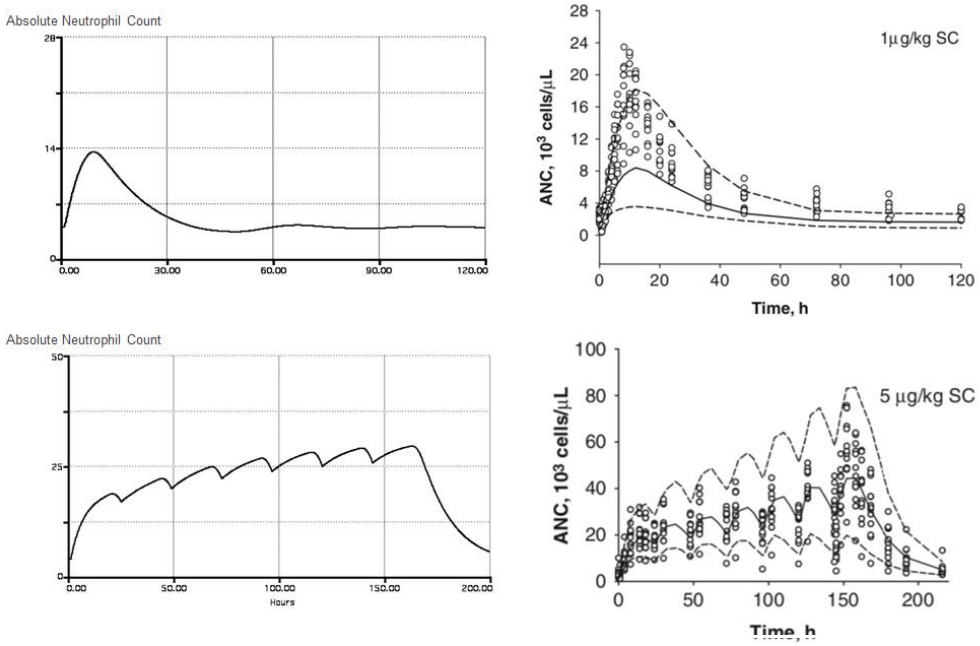

Figure 2: Comparative graphs of single G-CSF injection on the upper side and of seven daily injections below. (Model output (left) vs. Krzyzanski et al. (2010). For those graphs, points represent data taken, and the lines represent 5th, 50th and 95th percentiles of the model that authors proposed for that study)

Simulation experiments were carried out to analyze the critical dynamics of the system. It is found that G-CSF is the regulator of neutrophil production and mobilization for both mediate and immediate reactions. Immediate (inflammatory-like) reactions (Loop B1) work well for saving the patient for the moment and roots from the immediate transfer of neutrophils from the bone marrow neutrophil reservoir to circulation; but mediate (delayed) reactions (Loop B2 and B3) which root from the G-CSF stimulation of neutrophil production from stem cells should be timed with precision to generate an effective treatment regime to prevent neutropenia throughout the chemotherapy.

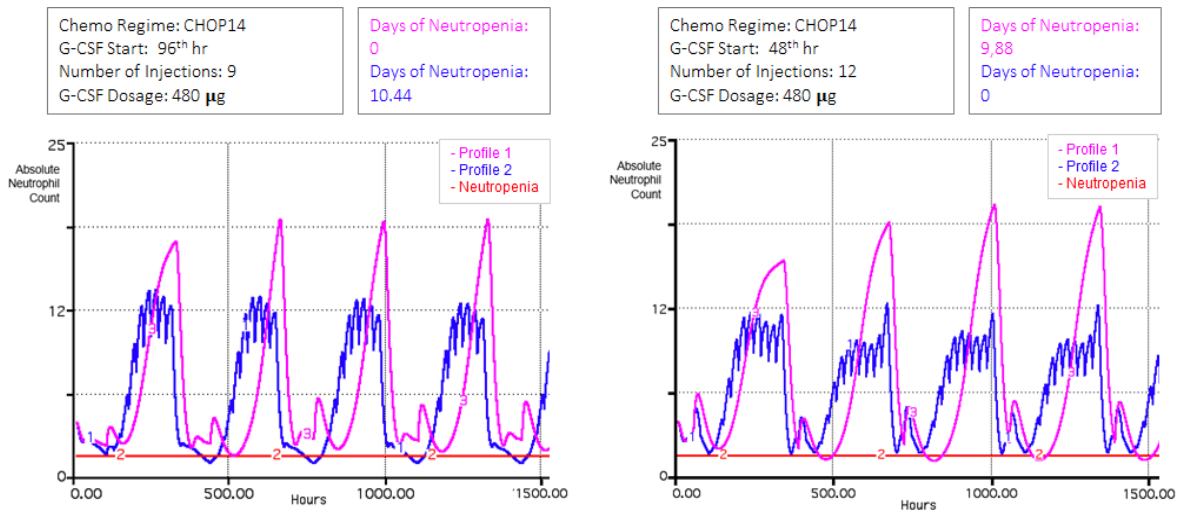

Figure 3: Two patient profiles under three G-CSF protocols

Using the high and low values for three major patient-specific parameters, several patient profiles were defined. Figure 3 shows the ANC responses of two example profiles (both experiencing neutropenia under standard G-CSF protocol) under two G-CSF protocols. A protocol efficiently keeping the neutrophil levels above the neutropenic level for one profile leads to nearly 10 days of neutropenia for the other profile, a lethal consequence.

Different G-CSF protocols were tested on each patient profile via a large-scale sensitivity run. Given the complexity of governing dynamics and the responses of different patient profiles to various protocols, it is concluded that the current state of the patient and physiological parameter variability among different patients are hard to overlook when designing a suitable G-CSF Protocol. Therefore, it is argued that customization of such protocols would provide a considerable improvement in decreasing the risk of neutropenia and ensuring the continuity of chemotherapy regimens without any interruptions.

Overall, the constructed model captures the hematological response to CIN accurately and can be used to analyze and understand the critical dynamics. In that sense, this study serves its purpose well in terms of a systemic examination of the influential factors of the system, accounting for the endogenous dynamic relations within. Moreover, the authors hope that introduction of system dynamics methodology to this topic will pave the way for further extensive studies of CIN treatment using G-CSF that would be objective-wise application-oriented like the SD study of Rogers et. al. (Rogers, Gallaher and Dingli, 2018) on red blood cells that is currently used as a decision support tool in determining personalized dosing regimes to prevent anemia in hemodialysis patients. Considering the proven success of such a study and similarity of the two structures, the future work on the management of CIN using G-CSF is expected to weigh on the development of patient-specific treatment regimes.

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