Chapter 14 Design of Drug Dosage Regimen (DDR) for Immune Thrombocytopenic Purpura (ITP) Patients Using Control Theory Concepts: A Simulation Study

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ABSTRACT

In this chapter, an optimal drug dosage regimen is designed by incorporating the standard treatment guidelines in terms of average and safe limits of drug dosage for immune thrombocytopenic purpura patients (ITP). If constant drug dosage is administered with fixed dosing, the interval leads to sustained oscillations of platelet count values with higher magnitude. Moreover, the amount of dose utilized for the treatment is also high. This leads to undesirable consequences which are dangerous to patients. Hence, a composite framework is essential to obtain optimal drug dosage for specific ITP patients. This chapter presents the potential benefits of the pharmacokinetic-pharmacodynamic (PK/PD) model of ITP patients and its applicability to obtain the optimum dosage profile using linear control theory in line with standard guidelines. Prediction of dosage interval is made for a specific patient using this PK/PD model. And this information is given to the controller framework as sampling time.

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Figure 1. Block diagram of patient PK/PD model and its application

INTRODUCTION

Drug delivery is the process of administering pharmaceuticals to the human body, including the drug's consequent effects on tissues and organs. Mathematical modeling of drug delivery can be divided into two different complementary approaches, the pharmacokinetic approach and the pharmacodynamic approach. Pharmacokinetics describes the effect of a drug in the body by recording drug absorption, distribution, diffusion, and excretion. Pharmacodynamics describes the effects of drugs in the body and is expressed mathematically through drug dose-body-response relationships. Usually, modeling of the drug delivery system requires a pharmacokinetic part, a pharmacodynamics part, and a link between the two. This PK/PD model is utilized for both pre-approval of a drug for clinical trial study and post-approval of the drug for dosage regimen design for specific inline with standard clinical guidelines as shown in Figure 1.

Chronic immune thrombocytopenia (Chronic ITP) is a condition of low levels of platelets in human blood. Platelets are those cells that help in clotting and control bleeding (Gilbert et al., 2020). The platelet count for a healthy individual is between 150,000 to 400,000 (150 to 400 x $10^{9}/L$) number of platelets per microliter (mcL). The platelet counts (PLT) less than $150x10^{9}/L$ is considered as an IITP patient. But the PLT less than $30x10^{9}/L$ is treated as severe ITP with a high risk of bleeding. A complete blood count (CBC) test measures the number of platelets in human blood.

Romiplostim is a suggested prescription medicine to treat patients with low blood platelet counts (thrombocytopenia) in adults with immune thrombocytopenia when the patients have an insufficient response to other treatments like corticosteroids, immunoglobulins, or splenectomy. The romiplostim injection helps prevent excessive blood loss, stops bleeding, and enhances the healing process (Bidika et al., 2020; Bussel et al., 2021; Christakopoulos et al., 2021; Selleslag et al., 2014). Kuter et al. (2013, 2020) presents the effects of romiplostim infusion and the significant improvements it brings in the

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