Semi-mechanistic modelling of neutropenia

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ABSTRACT
Population pharmacokinetics and pharmacodynamics PKPD modelling of chemotherapy-induced neutropenia can help with efficacy optimization and toxicity prevention in cancer patients. These medications focus on the fast-growing cells within the body and destroy them. Most of the fast-growing cells in the body are usually cancer cells, but there is an increased chance that certain healthy cells, such as white blood cells could be killed during chemotherapy. Several approaches have been identified for different drugs. Both empirical and mechanism approaches are discussed in this paper. Further, the author identified the pharmacokinetic-pharmacodynamic profile described by Friberg et al. (2003) as the most commonly used. This model consists of five sectors that represent proliferation, maturation, as well as elimination from the circulation of the neutrophils or leucocytes. This review covers these aspects and promotes a full understanding of dose prediction using semi-mechanistic modelling.

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INTRODUCTION

Most cancer patients stand a higher chance of succumbing to infection when exposed to chemotherapy-induced neutropenia. This form of medication inhibits the delivery of full-dose chemotherapy and prejudices the quality of life of a patient. Neutrophils, the most abundant leucocytes are responsible for providing primary defense for the innate immune system. Neutrophils achieve this role through phagocytosing, killing, as well as digesting bacteria. The number of neutrophils circulating in the bloodstream is reported as the absolute neutrophil count (ANC), and neutropenia is then defined by an absolute neutrophil count below a certain threshold. Population Pharmacokinetics studies otherwise referred to as pharmacodynamics PKPD facilitate learning about the unpredictability and effects of drug disposition. These studies also forecast the dose and other aspects of drug administration that can help patients maximize the efficiency and reduce the toxicity of a drug in the future (Rosner & Muller, 1997). By modelling, the data are summarized, predictions can be made, and a better understanding of the underlying physiology can be acquired. Concentration-effect relationships can be attained by fitting a prognostic PKPD model to the concentration as well as the effect observations. Either by simultaneous (it is possible to fit a model concurrently to all the data) or sequential (the model can first be fit to the PK data, followed by a fitting on the PD data,) (Zhang et al., 2003). The most predominant form of toxicity that is linked with the administration of anticancer drugs is myelosuppression. Quantitative relations were early established, such that when neutrophil counts fall below 1 x 10^9/L, the number of days with infection increases sharply, while few infections occur with neutrophil counts above this level. There are different approaches to model neutropenia. PD models proposed in neutropenia are empirical approach and a mechanistic approach (Friberg & Karlsson, 2003).
Empirical approach

The empirical approach is designed to describe the myelosuppressive effect of anticancer drugs. Since the observed drug concentrations and the observed myelosuppression are dissociated in time, a summarized pharmacokinetic variable of the exposure, such as the area below the plasma concentration against the time curve is often related to a summarized variable of the haematological effect (e.g. neutrophil counts at nadir or their ratio to pre-treatment basal counts). Linear, logistic regression and sigmoidal Emax models are examples of empirical models for myelosuppression that have been presented in several studies (Minami et al., 1995; van Groeningen et al., 1988; Zhou et al., 2000). The disadvantage of this approach is that the time course of drug concentration as well as the count of neutrophil is overlooked. Since the duration of neutropenia is not studied, it is of much interest since complications resulting from neutropenia rely on its duration as well as its extent (Bow, 2009).

Mechanist approach

The mechanistic approach, such as the models founded on physiology and pharmacology is superior to empirical models. The mechanistic approach is preferred over the empirical model since previous information can be used and is generally more dependable for extrapolation. A mechanistic model can be described as a mathematical model whose functioning is reliant on known or theoretical mechanisms of behavior of an organic system, where the parameters are in accordance with kinetic and physiological principles (Dahl et al., 2010). These models often require a large number of parameters, many of which may not be identifiable when analyzing clinical trial data. Mechanistic models can also be highly complex and therefore not suitable for analyzing data due to long runtimes and limited computational power. To be able to develop pharmacokinetic-pharmacodynamic models suited for estimations and consecutive predictions, it has been necessary to simplify the models, i.e. to make them semi-mechanistic. A number of semi-mechanistic models re-counting the time-course of myelosuppression have been published in the recent years (Minami et al., 1998; Zamboni et al., 2001; Friberg et al., 2002; Panetta et al., 2002; Panetta et al., 2003). These models have some common features, they all take into account the whole concentration-time profile, the use of specific compartments to represent the proliferating cells in the bone marrow and the circulating cells in the peripheral blood. They allow for estimation of the system and drug-related parameters, which give the advantage of relating the system parameters to the known physiology and predict different neutropenia descriptors depending on the question of interest. Neutrophil counts start to drop around ten days after chemotherapy (a period called nadir for which the risk of infection increases) (American Society of Clinical Oncology, 2019). Figure 1 shows the ability of a semi-mechanistic model to describe time at nadir, time to nadir, time to recover baseline and magnitude of the rebound. Since the complete pharmacokinetic profile is used to drive the models, differences in the pharmacodynamic outcomes can be observed for patients having the same AUC but different concentration profiles.

Examples of physiologically based models

There are several physiologically based models described by 1) Minami et al. (1998) 2) Zamboni et al. (2001) 3) Friberg et al. (2003) 4) Panetta et al. (2002) and 5) Bulitta et al. (2009). Minami et al. (1995) developed a model that records the time course of leukopenia after infusions of paclitaxel and etoposide. The model developed by Minami et al. (1998) assumed the generation of zero-order stem-cell. Besides, the model also featured sections for non-proliferating bone marrow precursor cell, as well as sections for peripheral blood. The impact of the drug was described based on the fraction of the stem-cell production that was being blocked. A related model was also evident in the study by Zamboni et al. (2001) where the researchers used a dose of topotecan to define the time course of neutropenia. Friberg et al. (2002) further extended the model that was introduced by Minami et al. (1998) and added parts to the many stages of the development of leukocyte in the bone marrow. The model by Friberg et al. (2002) also entails the negative feedback impact of G-CSF (granulocyte-colony stimulating factor). G-CSF is a growth factor that encourages the bone marrow to generate
more white blood cells. The authors used the model to define the time course of leukocytes after doses of 5-fluorouracil were induced in rats. They examined the effects of the drugs that only block the production of stem cells in precursor cells. For instance, whenever the drug is eliminated from the system, the process of stem cell production returns instantly to pre-drug exposure levels. In a study by Panetta et al., the authors adapted the models described before to include the effects of Temozolomide (TMZ). Through this modification, Panetta et al. (2002), developed a mathematical mechanism model of TMZ-induced myelosuppression. TMZ has a cytotoxic impact which causes a dose-dependent decrease in the rate of growth of precursor neutrophils in the bone marrow. In a different study by Bulitta et al. (2009), the authors established a mechanism-based pharmacodynamic model used to examine the time course of neutropenia among cancer patients who have been subjected to paclitaxel (Bulitta et al., 2009). This model works based on the cell lifespan concept and has myeloid cells in two stages in the bone marrow, including progenitor and mature cells, as well as the neutrophils within the circulating pool. An irreversible cytotoxic impact of paclitaxel on the progenitor cells located in the bone marrow plays a significant role in specifying the effect of the drug.

**CONCLUSION**

Currently, the most commonly used model to describe the pharmacokinetic-pharmacodynamic profile is that one first described by Friberg et al. (2002). This model is composed of five compartments (Figure 2) that represent proliferation, maturation (M1, M2 and M3) and elimination from the circulation of the neutrophils (or leucocytes). There is consistency in the system related parameter across various studies involving anti-cancer drugs as evident in the model (Friberg et al., 2002; Leger et al., 2004; Kesteren et al., 2005; Latz et al., 2006; Troconiz et al., 2006; Kathman et al., 2009; Puisset et al., 2007; Brain et al., 2008; Fetterly et al., 2008). This model has also been modified (e.g. extra compartment was added to the model) to account for certain aspects such as temporary increase in neutrophil count due to dexamethasone administration, effect of the high dose chemotherapy with support of peripheral blood stem cells (PBSC) and granulocyte colony stimulation factor external administration effect (reduction of MTT or a change in γ). The usefulness of this model has been shown by the creation of a tool for neutrophil guided dose adaptation in chemotherapy, the capability to establish animal to human predictions and in designing a model-based clinical trial for novel anticancer drugs.

**REFERENCES**


