Mechanistic models for myelosuppression

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Summary

As myelosuppression is the dose-limiting toxicity for most chemotherapeutic drugs, modelers attempt to find relationships between drug and toxicity to optimize treatment. Mechanistic models, i.e. models based on physiology and pharmacology, are preferable over empirical models, as prior information can be utilized and as they generally are more reliable for extrapolations. To account for different dosing-regimens and possible schedule-dependent effects, the whole concentration–time profile should be used as input into the pharmacokinetic–pharmacodynamic model. It is also of importance to model the whole time course of myelosuppression to be able to predict both the degree and duration of toxicity as well as consecutive courses of therapy. A handful of (semi)-mechanistic pharmacokinetic–pharmacodynamic models with the above properties have been developed and are reviewed. Ideally, a model of myelosuppression should separate drug-specific parameters from system related parameters to be applicable across drugs and useful under different clinical settings. Introduction of mechanistic models of myelosuppression in the design and evaluation of clinical trials can guide in the decision of optimal sampling times, contribute to knowledge of optimal doses and treatment regimens at an earlier time point and identify sub-groups of patients at a high risk of myelosuppression.

Introduction

Myelosuppression is the most common toxicity associated with the administration of anticancer drugs and infections remain a common cause of death in chemotherapy treated patients. Quantitative relations were early established, such that when neutrophil counts fall below $1 \times 10^9$/L, the number of days with infection increases sharply, while few infections occur with neutrophil counts above this level [1]. More predictive relations are still sought, where, for example, in a recent study it was shown after modeling, that the area between the curve for time versus leukocyte counts and the line of a leukocyte count of $2 \times 10^9$/L, were significantly larger for patients receiving neutropenic fever than for patients not experiencing fever [2]. Doses are consequently reduced and/or delayed in successive courses when chemotherapy-induced myelosuppression is observed. However, the reduction is usually made more or less empirically leading to a potential sub-optimal tumor effect.

In general, plasma concentrations are better related to the observed myelosuppressive effect than the dose of the cytotoxic drug. In 1977, a correlation between plasma concentrations of methotrexate and toxicity was shown [3], which led to that concentrations being routinely measured after administration of high-dose methotrexate, and an individualized regimen has also been shown to have a marked improvement on the outcome [4]. Also, today, with an increased computer capacity, more complex models can be established for drugs with less clear pharmacokinetic–pharmacodynamic relationships. In particular, modeling is becoming a useful tool in the drug industry to optimize treatment doses and schedules at an earlier time point. By modeling, the data are summarized, predictions can be made and a better understanding of the underlying physiology can be acquired. The relevance of pharmacokinetic–pharmacodynamic
Models to optimize cancer therapy was already pointed out a decade ago [5].

**Measurements of drug concentrations**

Observed drug concentrations and the observed effect, myelosuppression, are dissociated in time. Therefore, most of the pharmacokinetic–pharmacodynamic models of myelosuppression that have been published to date include a summary pharmacokinetic variable of the exposure related to a summary measurement of toxicity, usually percentage decrease of circulating leukocytes/neutrophils at nadir. Area under the concentration versus time curve (AUC) [6], steady-state concentration (Css) [7] and time above a threshold concentration [8] are examples of commonly used summary variables of the exposure. All such summary variables suffer from counterintuitive predictions. For example, when AUC is used as a summary variable, it would actually mean that a bolus injection produces the same myelosuppressive effect as an infusion with a very low concentration during infinite time, as long as the AUC is the same. On the other hand, when the time above a threshold concentration is related to the effect, an all-or-none relationship is predicted. This means that if the concentration is just below this level, there is no effect, while if the concentration is just above this level, the effect is at its maximum. It is more likely that in reality the underlying relation is somewhere in between these two extremes and therefore it is superior to estimate the best summary of the concentration–time profile [9], estimate the sensitive time of drug exposure [10] or to directly apply the whole concentration–time profile [11]. Then, different doses and administration schedules are more accurately accounted for, as many chemotherapeutic drugs have a schedule-dependent toxicity [12].

**Measurements of myelosuppression**

In many studies, the myelosuppressive effects are just summarized in terms of the fraction of patients at different dose levels or schedules with Grade III and/or Grade IV neutropenia. For most established pharmacokinetic–pharmacodynamic relationships, exposure is related to the absolute or relative decrease of blood cells at nadir, but since measurements are usually made only once or twice a week, it is not likely that the real nadir is observed. In such analyses, the nadir is overestimated, measurement errors are not appropriately accounted for, interindividual variability is inflated and information of the duration of myelosuppression is wasted. To partly take this into account, summary variables of the myelosuppression like “area between the curves” [13] have been used in analysis of myelosuppression. Then, both the decrease and the length of time of its occurrence are taken into account. Time to nadir [14] and number of days below a certain neutrophil value [13] are also examples of other summary variables of myelosuppression. However, modeling the whole time-course of myelosuppression leads to a greater understanding of the effects of chemotherapeutic drugs on the bone marrow and a few studies have implemented this [2,9–11,15–19].

Pretreatment count has been shown to be a predictor of leukopenia [20,21]. Survival fraction [22] or percentage decrease [6] is therefore often used, even though it assumes that the baseline is time-invariant and a single measurement can adequately describe it. In addition, since it is the absolute counts that are related to the incidence of neutropenia and neutropenic fever [1], it might be preferable to model the absolute counts, which in practice means also estimating the baseline count [11].

**Empirical models of myelosuppression**

To estimate the magnitude of myelosuppression, linear models [23], log-linear models [24], logistic regression models [25], basic $E_{\text{max}}$-models [26] and sigmoid $E_{\text{max}}$-models [6] are commonly used to describe the relation between exposure and a summary variable of myelosuppression. In addition, a more general model has been presented [9], which relates the exposure to a direct effect (effect on bone marrow cells in this case), and the cumulative direct effect is related to the observed effect.

To describe the whole time-course of leukopenia, Rosner et al. [15] modeled the change of the logarithm of leukocytes after cyclophosphamide administration. Three mathematical functions were used; a horizontal line corresponding to the patient’s baseline, a straight line with negative slope described the decline in leukocytes until the time of nadir and an S-shaped, logistic curve, characterized the phase of recovery. They used the dose as input to their model and neglected pharmacokinetics. Karlsson et al.