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New horizons in cytotoxic therapeutic drug monitoring

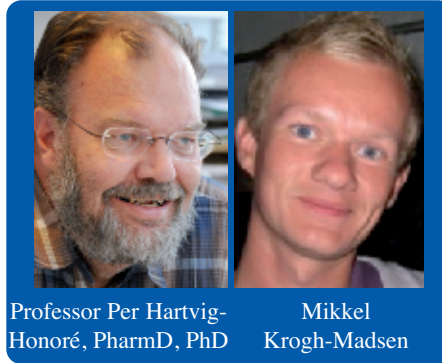
In many cancers, cytotoxic drugs have only a marginal long-term effect and resistance develops quickly. Optimal dosing is needed and drawbacks exist with traditional dosing calculations. Therapeutic drug monitoring (TDM) using population-based methods may hold promise to optimise therapy.

Dosing of cytotoxic drugs

Cytotoxic drugs are characterised by a narrow therapeutic margin with high toxicity, causing many and severe side effects. This points to the obvious need for therapeutic optimisation.

Most doses of cytotoxic drugs are empirical, coming from previous experience and mainly tailored to avoid the most serious toxicity. There is an obvious large variation in the disposition of these drugs not just between patients but even within the same patient on different occasions. The variation in tumour response can partly be imposed by the variability in disposition. The pharmacokinetics and pharmacodynamics (PK-PD) is influenced by age, comorbidities and other patient-specific factors. Cytotoxic drugs may act as pro-drugs and may have active metabolites. This has to be taken into account when dealing with the pharmacokinetics of cytotoxic drugs. The tumour usually exhibits genetic polymorphism conferring a certain degree of drug resistance. Furthermore, blood supply for many tumours is highly irregular due to malfunctioning of blood vessels in the microenvironment surrounding the tumour. On both the disposition side and effect side there are interactions with endogenous and exogenous substrates in and around the tumour. The cytotoxic effect is difficult to measure and usually it takes a long time before it becomes obvious. The effect measures are difficult to quantify, although techniques using biomarkers or imaging with positron emission tomography might be useful.

Dosing of cytotoxic drugs is usually based on body surface area (BSA) and in the last 50 years most chemotherapy doses have been individualised according to this measure. There are several problems related to dose adjustment by BSA. Indeed, most studies have shown that BSA-based dosing does not reduce pharmacokinetic variability. Furthermore, BSA does not account for different body compositions, organ function, activity of metabolising enzymes, drug resistance, sex, age, concomitant diseases or co-administration of other drugs. There is also no relation between BSA and tumour size and type, or for accessibility of the drugs to the tumour. These difficulties with current practice warrant a change in dose adjustment routines. Other methods such as dosing per body weight or even flat dosing have, as expected, not improved the tailoring of dose.



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Therapeutic drug monitoring of cytotoxic drugs

TDM means that therapy is followed by plasma concentration measurements and dose is adjusted accordingly. It is used for drugs with a narrow therapeutic margin, and for drugs with large inter- and intra-individual variations in dose – concentration relationships because of formulation, drug interactions, lifestyle, comorbidities, and also genetic variation in metabolism. The requirement to use TDM is when there are:

- no direct clinical measures that provide clear evidence of efficacy or toxicity
- therapeutic or toxic effects that are clearly related to plasma concentration of the drug
- drugs with a narrow therapeutic window
- drugs that are used for prophylaxis, e.g. epilepsy, mania, diabetes
- drugs that do not form active metabolites.

TDM is used to adjust the dose from the plasma concentration in order to achieve maximum effect and minimise drug-related toxicity, to monitor ongoing therapy and also to indicate patient compliance. TDM is routinely performed in the clinic for epilepsy drugs (phenytoin, carbamazepine), lithium, digitalis, cyclosporin and most antibiotics.

Can TDM significantly affect cytotoxic drug therapy? Yes, since it predicts toxicity better in some cases and increases efficacy in other cases. TDM gives an increased understanding of the large patient variability encountered regarding responses to drugs. Yet TDM is not used routinely for cytotoxic drugs. In fact, it is only commonly used for methotrexate. However, there is also long-term follow-up on 6-mercaptopurine in children with acute lymphoblastic leukaemia, as steady-state concentrations that are not high enough are associated with an increase in relapses. There is also some interest in monitoring 5FU as well as the new drugs for chronic myelogenous leukaemia and metastatic renal carcinoma. There are several reasons for this including:

- a lack of established therapeutic ranges
- a poor understanding of dose-concentration-response relationships
- a time lag between drug measurement and clinical effect.

TDM has not found its way into clinical oncology. Cytotoxic dosing is much more complicated than dosing for non-onco-

logical treatments. Good efficacy and low toxicity depend on an array of factors related to the individual patient, the cancer type itself and its genetic properties, and the tumour burden. Indeed, statistical methods exist to account for all these factors in the analysis of the optimal dose for any given patient. Population-based PK-PD, one such statistical approach, is increasingly being investigated in the field of oncology.

Population-based methods to optimise therapy

Population-based PK-PD models seek to determine how patient factors affect not just exposure to a drug but their response as well. The models, through the use of sophisticated software, simulate different dose regimens and treatment options. Indeed, such services are of importance to the pharmaceutical industry, with the aim of providing useful information from clinical studies in terms of how patients react to drugs. For example, by better identifying appropriate dose regimens fewer clinical trials may be needed, thus saving money.

More knowledge about cytotoxic PK-PD and the introduction of Bayesian modelling to aid in the prediction of optimal dosage of cytotoxic drugs may improve therapy outcome. Bayesian estimations have allowed for fine-tuning of doses as well as administration schedules to be accurately adjusted for cytotoxic drug therapies. It goes without saying that predictive methods and more individualised therapy are of value in optimising treatment outcomes. The ability to model PK-PD relations in the individual patient may optimise dosing of cytotoxic drugs with respect to both dose and dose intensity.

The advantages of population-based methods are that data from all patients given cytotoxic drugs can be modelled simultaneously in a population non-linear mixed effects analysis. The data include all information of cytotoxic drug kinetics in the patient, patient characteristics, disease properties, as well as effects on the tumour or encountered side effects. This method treats the population, rather than the individual, as the unit of analysis. By doing so, sparse data from many individuals can be analysed, and a more representative sample of the target population is obtained. It is possible not only to describe the mean tendencies in the population, i.e. the typical values, but also to describe the random effects, including variability between subjects, between occasions, and within a subject (residual variability). The model-building process is performed in a stepwise fashion. Covariates are entered in the

model by forward inclusion and backward deletion. The procedure is to include all covariates one by one into the basic model and retain the model with the covariate-parameter relation causing the largest significant improvement in the objective function value. Several criteria are used to validate the resulting model, e.g. objective function values and best goodness of fit. This model serves as the new basic model and the stepwise inclusion procedure is repeated until no significant improvement is seen and this model then constitutes the full

model. In the backward deletion the covariates in the full model is eliminated one by one until no more covariates can be eliminated from the full model without causing a significantly detrimental effect to the model fit. The computer software NONMEM (nonlinear mixed effect modelling) is usually used.

Conclusion

A better knowledge of the relationships between pharmacokinetic parameters or drug exposure variables, tumour growth, and treatment outcomes may improve treatment efficacy and patient outcomes by using *a priori* determination of the first dose and *a posteriori* Bayesian adjustment of the subsequent doses using population-based methods. Such models have the potential to eliminate many of the difficulties associated with BSA-based dose

adjustments. Patient characteristics are used in the model to provide suggestions for optimal dosing of cytotoxic drugs. The method has shown success in several studies and is also used routinely to improve therapy. This is the way to reach the difficult goal of individualised and tailored dosages for optimal therapeutic results in the individual patient. The benefit of the population-based method promises to be optimisation of cytotoxic drug dosages, leading to better efficacy, fewer side effects, and more cost-effective treatment.

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