

Therapeutic drug monitoring of cancer chemotherapy

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Therapeutic drug monitoring is not routinely used for chemotherapy agents. There are several reasons, but one major drawback is the lack of established therapeutic concentration ranges. Combination chemotherapy makes the establishment of therapeutic ranges for individual drugs difficult, the concentration-effect relationship for a single drug may not be the same as when that drug is used in a drug combination. Pharmacokinetic optimization protocols for many classes of cytotoxic compounds exist in specialized centers, and some of these protocols are now part of large multicentre trials. Nonetheless, TDM clearly has the potential to improve the clinical use of chemotherapy agents, most of which have very narrow therapeutic indices and highly variable pharmacokinetics. A substantial body of literature accumulating during the past 15 years demonstrates relationships between systemic exposure to various chemotherapy agents and their toxic or therapeutic effects. This article reviews TDM concepts in addition to tools based on pharmacokinetic modeling of chemotherapy agents. The administered dose of chemotherapy agents is sometimes adjusted individually using either a priori

or a posteriori methods. These models can only be applied by using the same dose and schedule as the original study. Bayesian estimation offers more flexibility in blood sampling times and, owing to its precision and to the amount of information provided is the method of choice for ensuring that a given patient benefits from the desired systemic exposure. Moreover, the role and application of Pharmacogenetics as a tool for individualizing chemotherapy is discussed highlighting the agents and mechanisms that have been well studied and defined and their relevance to clinical practice. Finally, this paper addresses issues critical to the optimal use of TDM in a clinical setting, and the role of clinical pharmacist in this regard. In addition, it discusses future developments in this field that can contribute to improving cancer chemotherapy in terms of patient outcome and survival. *J Oncol Pharm Practice* (2007) 13: 207–221.

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INTRODUCTION

Therapeutic drug monitoring (TDM) has been utilized in the clinical care of patients from the early 1960s. It involves the measurement and interpretation of drug concentrations in biological fluids

and the individualization of drug dosages or schedules to maximize therapeutic outcomes, minimize toxicities, or both.¹ In theory, a drug should fulfill several criteria in order for TDM to be valuable. These include presence of considerable inter- or intra-individual pharmacokinetic variability, existence of a defined relationship between concentration and pharmacological effects, a narrow therapeutic window, and the availability of a defined and accurate method for drug quantification in biological fluids.^{2,3} TDM is broadly applied to a diversity of drugs from

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different therapeutic classes, such as cardiovascular agents, antiepileptics, antibiotics, respiratory smooth muscle relaxants, and anti-inflammatory agents, some cancer chemotherapeutic agents, immunosuppressants, and antidepressants. In the midst of all these therapeutic classes, TDM has limited use with antineoplastic agents. Anticancer agents are generally characterized by a large inter-individual pharmacokinetic variability; relationships linking toxicity to systemic exposure, and toxic effects better related to exposure than to dose or dose intensity. Consequently, TDM can be and has been successfully applied to optimize anticancer treatments including carboplatin, methotrexate and 5-FU as well as etoposide, and 6-mercaptopurine.^{4,5-10}

LIMITATIONS OF TDM FOR CANCER CHEMOTHERAPY

The clinical value of TDM for antineoplastic agents is at this time restricted by several factors.¹¹⁻¹³ First, there exists an imperfect understanding of the pharmacology and pharmacokinetics of most antineoplastic agents. Second, the plasma drug concentration is an indirect measure of the amount of drug in the target tissue, because the site of action is frequently distant from intravascular spaces in addition to the fact that solid tumors may have their own unique blood supply. Third, there is naturally a long lag time between the measurement of drug in plasma and evaluation of the definitive pharmacodynamic effect, which is usually, cure. If improvement in cure rate is used as the outcome variable this usually requires at least 5 years of follow-up to dependably evaluate the outcome. Consequently, studies require more time and more complex process that is significantly different from that of studies for drugs with quicker effects, such as antibiotics. Fourth, the difficulty in identifying concentration-effect relationships because antineoplastic agents are almost always given in combination.¹⁴ Therefore, it would be very difficult to accurately define the pharmacodynamics of each individual agent. In addition, combination therapy also complicates the pharmacodynamics of drug toxicity.

Fifth, cancer is a group of heterogeneous diseases, with inherent characteristics that affect the concentration-effect relationship for antineoplastic agents. They display heterogeneity in blood supply and cellular characteristics, leading to different levels

of sensitivity and resistance to antineoplastic agents.¹⁵

Only few agents fulfill all the TDM prerequisites because of the lack of well-defined relationships between efficacy and systemic exposure. Such relationships have been demonstrated only for very few drug/disease couples, for example methotrexate and acute lymphoblastic leukemia (B lineage), carboplatin and ovarian cancer,¹⁶ and 5-FU and metastasis colorectal¹⁷ or head and neck cancer.^{18,19}

POTENTIAL BENEFIT OF TDM FOR CANCER CHEMOTHERAPY

Many clinical cancer trials show the benefits of maximum chemotherapy intensity¹⁴ signifying the need to treat patients with doses that will produce concentrations in the upper end of the nontoxic range to increase likelihood of response or cure. If toxic plasma concentrations can be defined for each agent, then TDM could be useful in identifying which agents are being overdosed or under dosed in any given regimen.

TDM in cancer chemotherapy has additional advantages besides individualizing chemotherapy to improve efficacy and avoid toxicity; these include enhancement of compliance, minimization of pharmacokinetic variability among patients, dose adjustment in patients with hepatic and (or) renal dysfunction,¹⁵ and detection of drug interactions.³

Despite the limitations facing TDM application for antineoplastic agents, there exists vast potential for advancement of cancer treatment if TDM can be appropriately practiced. Antineoplastic agents satisfy the criteria for TDM: vastly variable pharmacokinetics and narrow therapeutic indices. In addition, when treating patients with cancer disease, seeking the highest efficacy from chemotherapy is an important principle because of the magnitude of the consequences to cancer patients. Sub-optimal therapy can greatly reduce the probability of cure for curable cancers. On the other hand, side effects, such as myelosuppression, can be life-threatening and may be related to higher than optimal therapy. Consequently, a therapeutic range that defines efficacy concentrations as well as toxicity concentrations would have enormous clinical utility.

PHARMACOKINETICS AND PHARMACODYNAMICS OF CHEMOTHERAPY

Drug pharmacokinetics depends on the four basic processes namely—absorption, distribution, metabolism, and elimination. These processes differ between patients and result in substantial differences in plasma concentrations for the same dosage given to different patients. Moreover, variability can also be observed in pharmacokinetics as a result of day-to-day changes in an individual patient's ability to metabolize or excrete a drug. Intra-patient variability can be explained in-part by patient noncompliance, drug interactions, and in all cases will require tailoring dosages to fit the current needs of the specific patient.

The concentration of drug in plasma does not always reflect the concentrations at the cellular level, which is the site of action for most drugs; however, it is typically difficult or impossible to measure. Pharmacodynamics also exhibits wide inter- and intra-individual variability. In practice, plasma drug concentrations usually provide an accessible measurement for defining the pharmacokinetic parameters, such as systemic clearance, steady-state plasma concentration (C_{ps}), and area under the concentration-time curve (AUC).

THE CONCEPT OF DOSE-INTENSITY AND SYSTEMIC EXPOSURE

The concept of dose-intensity was first advocated by Hryniuk and Bush,²⁰ from breast cancer clinical trials data. Dose-intensity is defined as the amount of drug given per unit time (eg, mg/m² per week), and is based on the postulation that dose scheduling or infusion time does not directly determine tumor cell kill, which may not hold true for many antineoplastic agents. Furthermore, it grants equal importance to time delays and dose reductions.²¹ It is vital only for tumors responsive to the medications being evaluated, where the dose-response curves is often steep, and an increase in the dose or dose-intensity would lead to improved clinical effects.²²

The concept of systemic exposure has been studied as an alternative to dose-intensity for anti-cancer drugs.^{11,23} It is presented as a potentially more useful measurement of dose-intensity.¹¹ C_{ps} and AUC are PK parameters that can be used

to measure systemic exposure to a drug. For instance, in the treatment of osteosarcoma, where 4- or 6-h MTX infusions are usually administered, peak plasma concentration at the end of the infusion was shown to be linked to efficacy.^{24,25}

In case of drugs that metabolize to active intracellular metabolites, eg, mercaptopurine (MP) and MTX, concentrations of their active metabolites in surrogate cells (eg, erythrocytes) have also been used to measure systemic exposure.

Several different applications of systemic exposure have been used in cancer treatment. The European Organization for Research and Treatment of Cancer (EORTC) Pharmacokinetics and Metabolism Group proposed a guided dose increase in phase I clinical trials to assist determinations of the maximum tolerated dose (MTD) for investigational anticancer drugs.^{26,27} Soon after, a newer concept named the maximum tolerated systemic exposure (MTSE) was proposed as a move forward to MTD for phase I and II clinical trials of antineoplastic agents.^{28,29}

For a few schedule-dependent drugs such as etoposide, it has been found that more complex indices are more appropriate. Etoposide is a cell-cycle specific cytotoxic drug, that means that the cells have to be exposed to it during the sensitive part of the cell cycle (late S-phase) and exposure maintained for long enough to kill the cells. The therapeutic window is highly dependent on the duration of the infusion. Duration above a certain threshold concentration was found to be the best predictor of efficacy in small-cell lung cancer.⁸

Over the past 15 years, studies have been done to establish the association between systemic exposure and therapeutic outcomes. Many studies of pharmacodynamics of numerous cancer chemotherapeutic agents are performed and reviewed in greater detail elsewhere.^{13,30-35}

EVALUATION OF THE RESPONSE

The predicted response is more often toxicity than efficacy. Severity scales have been defined for some types of toxicity (eg mucositis and diarrhea), while quantitative measurements to evaluate hematological toxicity are available. Efficacy can be evaluated through a near-immediate response, such as tumor necrosis³⁶ or tumor activity (using sophisticated methods, such as positron emission tomography scan, or PET-scan) or through a long-term response,

such as time to progression, continuous time without relapse, or survival time. However, the latter data are much more difficult to obtain.

METHODS FOR DOSE INDIVIDUALIZATION AND TDM OF ANTICANCER AGENTS

The methods used for individual dose adjustment can be classified into three categories:

(i) *a priori* methods, (ii) test dose method, (iii) *A posteriori* methods.

(i) *A priori* methods

A priori methods allow the estimation of the dose necessary to reach a target exposure in a given patient using morphological, biological, and physiological data, such as body weight, age, gender, serum creatinine level, and glomerular filtration rate (GFR). The design of such a formula requires a close relationship between an estimated parameter and a pretreatment factor. The most frequently used formulae are those for carboplatin.³⁷⁻⁴³ Both Calvert's⁴¹ and Chatelut's⁴³ formulae have proved their applicability and their efficiency. With Calvert's formula, the dose necessary to achieve a target AUC (between 3 and 8 mg/mL) is calculated using the GFR. Chatelut's formula which was developed using pharmacokinetic modeling only requires age, gender, and weight and serum creatinine level and is particularly appropriate for outpatients. The impact of population pharmacokinetic modeling on *a priori* dose adjustment can also be illustrated by studies dealing with topotecan,^{42,43} which showed close relationships between topotecan clearance and renal function (serum creatinine or creatinine clearance), and body size. These population studies suggested *a priori* dose adjustments on the basis of these individual factors but, as they were not entirely validated, the relationships proposed deserve further prospective evaluation.

Even though *a priori* methods are simple to implement and somewhat balance for the inter-individual pharmacokinetic variability, their predictive performance is not as good as that of *a posteriori* methods.⁴⁴ Typical average bias and precision of <10 and 20%, respectively, can generally be expected with these methods.

(ii) The Test-dose Method

This method includes two steps: first, the individual pharmacokinetic parameters are determined after

administration of a bolus injection of a moderate dose using multiple blood samples; second, these parameters are used to calculate the full dose necessary to achieve the target exposure. The principle of this method is much debated because it can be used only when the pharmacokinetics are linear and always involves additional blood samples and a delay before efficient treatment is begun. This method is very often used for MTX as it requires dose adjustment most routinely because of its very large inter-individual pharmacokinetic variability (drug concentration as well as total clearance can vary over a 5-fold range from one patient to another after administration of a standard fixed dose).⁴⁵⁻⁴⁷

(iii) *A Posteriori* Methods

a. Nomograms

Nomograms have been routinely used for individual dose adjustment of fluorouracil (5-FU). The abscissas represent the observed AUC_{0-48h} values and the ordinate is the decrease (as a percentage) in dose needed to reach the full target AUC.

For example, Santini *et al.*¹² developed such an approach: they measured AUC in the middle of a 5-day infusion and then proposed to adjust the dose of 5-FU in order to maintain the full AUC, which is reached at the end of the infusion, under the toxic threshold. The benefit of 5-FU dose adjustment with a similar method in patients with head and neck carcinoma has been well demonstrated in a trial comparing it with a standard fixed dose.⁴⁸ The response rate was similar in the two arms while the mean administered dose and toxicity were reduced in the nomogram arm.

b. Multilinear regression (MLR) Methods

Multilinear regression models aim to evaluate one exposure variable (mainly AUC) using very few (generally two or three) blood samples collected at particular times. Exposure is often described as a linear function of the concentrations measured at particular time-points.

MLR is not based on a pharmacokinetic model and the equation results only from correlations (and cross correlations) between certain sampling times and the exposure index studied. Such methods have been proposed to monitor the AUCs of a few drugs and metabolites, for instance etoposide, doxorubicin, carboplatin, cyclophosphamide, topotecan, irinotecan, and metabolites.⁴⁹⁻⁵⁸ However, as far as anti-cancer drugs are concerned, these methods are generally not regarded as sufficiently precise for TDM. Additionally, they are hardly compatible with routine clinical practice because of the requirements

for intense blood sampling which is not appropriate for routine clinical care.

c. Maximum *a posteriori* (MAP) Bayesian methods
Maximum *a posteriori* Bayesian estimation methods require a pharmacokinetic population model and a few concentration data collected after or during administration of the drug. In addition, physiological or biological figures are also used in the calculation. In the past, the two-stage approach was the method most often used in oncology to describe population pharmacokinetics. The first stage is the estimation of each patient's pharmacokinetic parameter values, using nonlinear regression or maximum likelihood estimation and a full concentration profile. In the second stage, the mean and standard deviation of each parameter, as well as the correlation and covariance of each parameter with the others, are calculated. This modeling method is simple but requires multiple blood samples from each patient and leads to overestimation of the inter-individual as well as the residual variability.

In contrast, the one-stage method is true population modeling. The data observed in all patients are considered as a whole, so that it is possible to scatter the different sampling times amongst several patients, to the point that each patient can even undergo only one blood sampling. The most frequently used method is called the non-linear mixed-effect model. It is a parametric method. Inter-individual pharmacokinetic variability can sometime be partly explained by individual factors or covariates that may be very easy to obtain, such as age, gender, or weight. Thus, this population approach provides information on which covariates are important in determining the pharmacokinetics of the drug and how much variability can be explained by them. This method mixes fixed effects (such as doses, covariables, and population parameters, taking eventually into account the effects of covariables on concentrations) and random effects (ie the intra-individual variability and the unexplained part of the inter-individual variability). Non-linear mixed-effect modeling is increasingly used for one-stage pharmacokinetic as well as pharmacodynamic population modeling. The most powerful and generally employed program using this approach is NONMEM.⁵⁹ In the non-parametric methods,^{60,61} the population pharmacokinetic parameters are not constrained to some assumed distribution but are described by the observed distribution itself. Consequently, these methods are able to discover, with no external help, unsuspected subpopulations

which could be missed using parametric techniques. NPEM⁶²⁻⁶⁴ is the only program using this approach that has been employed in oncology.

MAP Bayesian estimation has been used for TDM for 30 years. This strategy takes into account the pharmacokinetic characteristics of a typical population, in a statistical form on the one hand, and fractional data collected in the studied patient, such as one or two plasma drug concentrations and body weight on the other.

MAP Bayesian methods have major advantages over other strategies, as they allow:

- (i) Visual checking of modeling efficiency, by looking at the concordance between the measured concentrations and the predicted concentration-time curve.
- (ii) Estimation of several pharmacokinetic parameter values and exposure indices simultaneously.
- (iii) Flexibility with respect to the sampling times rendering this method more relevant to real life and the constraints of a clinical department.
- (iv) Inclusion of new data in the population database allows progressive refinement of the population pharmacokinetic model.

The main drawback is that such an estimator is difficult to develop, but it is easy to use. Bayesian estimators were developed for a large number of anticancer drugs: methotrexate,⁶⁵⁻⁶⁸ carboplatin,⁶⁹⁻⁷² cisplatin,⁷³ etoposide,^{74,75} teniposide,⁷⁶ anthracyclines (doxorubicin and pirarubicin),⁷⁷⁻⁷⁹ irinotecan,^{80,81} topotecan,^{43,82} vincristine,⁸³ vinorelbine,^{84,85} and suramin.^{86, 87}

Generally two or three blood samples were enough to predict individual pharmacokinetic parameter values with low bias and good precision. Few of these estimators have been used, whether in controlled exposure clinical trials or in routine practice, for example for monitoring methotrexate,⁶⁵ carboplatin,⁶⁹⁻⁷² and suramin.^{86,87} Bayesian estimation allowed doses, and sometimes the administration schedule, to be accurately adjusted. Moreover, good control of toxicity and very few major toxic events (despite a frequent increase in the mean administered doses compared with fixed standard doses) were generally reported.

The implementation of TDM in clinical practice can be illustrated with the examples of many anticancer drugs. MTX is still the drug for which plasma

concentration monitoring is the most routinely used, with two distinctive aims: (I) MTX TDM;⁶⁶ (ii) individual dose adjustment of folinic rescue.⁶⁷ Bayesian adaptive control strategies have been successfully used to adjust MTX dose in real time during 24-h as well as 8-h infusions. In the comparative trial by Evans *et al.*,¹¹ MTX clearance was estimated on the basis of plasma concentrations 1 and 6 h after the start of the infusion, and the dose was eventually adjusted at 8 h to achieve the target range exposure. Pignon *et al.*⁶⁸ used dose adjustment at 6 h, using samples collected at 4 and 5 h, to reach concentrations of 5×10^{-4} or 10^{-3} M at the end of an 8-h infusion. Another study performed in children who received 24-h MTX infusions,⁶⁵ Bayesian forecasting was employed to adjust the dose of folinic acid, used as an antidote. A single blood sample (collected at 48 h) was shown to be sufficient to predict the time at which the MTX concentration reached a predefined threshold below which the administration of folinic acid could be stopped (ie 0.2 mol/L).

Chatelut *et al.*¹⁴ reported successful dose adjustment of carboplatin in adults with germ cell tumors. Each patient received a 1-h infusion each day for 4 days. The first dose was calculated using the *a priori* Chatelut's formula⁴⁰ in order to reach a daily AUC of 5 mg/min/mL, and was sometimes modulated according to the patient's status. The interdose AUC was observed on days 1 and 2 and the dose was readjusted using Bayesian estimation on days 3 and 4, in order to obtain a total AUC of 20 mg/min/mL. The Bayesian estimator used was based on a population model obtained using NONMEM and took into account body surface area, body weight, age, serum creatinine level, gender, and two serum concentrations corresponding to samples collected about 1 and 4 h after the end of infusion. The results were very good as all patients effectively received a total AUC very close to the target value. The first clinical interest of this TDM method for such intensified chemotherapies was a good control of toxicity.

Nguyen *et al.* attempted to use a population analysis for the identification of patient covariates that might appreciably influence vinorelbine disposition and also tried to define a limited sampling strategy for further Bayesian estimation of individual pharmacokinetic parameters. The population pharmacokinetic model was built in a sequential manner on a subset of two-thirds of the data, starting with a covariate-free model then progressing to a covariate model using the nonlinear-mixed effect methodology. The remaining one-third of the data was used to validate several sparse sampling designs. It was found

that a linear three-compartment model characterized vinorelbine blood concentrations. Two primary pharmacokinetic parameters [total clearance (CL) and volume of distribution (Vd) were related to various combinations of covariates. The relationship for total clearance was dependent on the patient's body surface area (BSA), weight (Wt), serum creatinine (Cr_s), and platelet count before administration (Plt). The optimal limited sampling strategy consisted of a combination of three measured blood concentrations; the first immediately before the end of infusion or 20 min later, the second at either 1, 3, or 6 h and the third at 24 h after drug administration.^{88,89}

Urien and Lokiec investigated the pharmacokinetics of unbound and total plasma platinum using a population approach in order to identify patient characteristics that may influence the disposition of the cisplatin. Pharmacokinetic and demographic data were collected from adult patients treated with 30-min daily infusions of cisplatin for various malignancies. Unbound and total platinum concentration-time data were analyzed using a nonlinear mixed effects model. A linear two-compartment model best described total and unbound platinum plasma concentration-time data. Unbound clearance was dependent on BSA and creatinine clearance, and Vd was dependent on BSA. The pharmacokinetic parameter, $f(m)/V(m)$, a measure of the clearance of unbound platinum due to irreversible plasma binding, was related to serum protein concentration and to the inverse of dose per $m(2)$. The covariate modeling of CL, Vd(1), and $f(m)/V(m)$ improved the inter-subject variabilities associated with these parameters. The final pharmacokinetic models were validated using 200 bootstrap samples from the original datasets.⁹⁰

On the other hand, de Jongh *et al.* characterized cisplatin population pharmacokinetics in adult cancer patients by a one-compartment linear model with BSA as the only significant covariate that impacted on both CL and Vd with the use of NONMEM, performing generalized-additive modeling to identify candidate covariates.⁹¹

Kellie *et al.* reported the results of their work which was done to investigate the pharmacokinetics of docetaxel (40 mg/m² week using sparse concentration-time data collected from patients with advanced cancer and studying the relationships between docetaxel clearance and 21 covariates. They followed a population pharmacokinetic approach to analyze plasma concentration-time data and the mean population and individual *posterior* Bayesian estimates of docetaxel clearance were estimated

using P-PHARM. Significant relationships were found between clearance and $1/t_{\max}$ and several of the liver function enzymes. This model provided both precise and unbiased predictions of docetaxel concentrations in a validation group of patients and an estimate of the population mean.⁹²

Earlier work by Launay-Iliadis *et al.*, which was two population analyses on short i.v. infusion of docetaxel, one using nonlinear mixed-effect modeling (NONMEM) and the other using nonparametric maximum-likelihood (NPML) sequentially to determine the structural model; estimate the mean population parameters, including clearance (Cl) and inter-individual variability; and find influences of demographic covariates on them. They found that a three-compartment model gave the best fit to the data and the final NONMEM regression model for expressed Cl (in liters per hour) directly as a function of BSA.⁹³

EVALUATION OF THE IMPACT OF THERAPEUTIC DRUG MONITORING

Numerous studies have evaluated the effect of individual dose adjustment by studying the percentage of patients who achieved a target exposure, which may support the performance of the pharmacokinetic parameter value forecasting, but is not sufficient to demonstrate the relevance of TDM. Relevance of adaptive control methods has to be studied from a clinical point of view because physicians need to 'treat the patient and not the concentration'.⁹⁴ Individual dose optimization is based on relationships between systemic drug exposure and therapeutic end-points (tumor response, toxicity, and survival), which helps to define a target range of exposure, but the benefit of adaptive administration has to be evaluated prospectively. Two exciting approaches have been used in oncology: a direct and a more indirect one. The direct approach studied the impact of TDM on patient outcomes and, in randomized trials, compared treatment responses (such as survival at a given time, relapse rates, frequency, and severity of toxic events) after individualized dose adjustment and after administration of standard fixed doses.^{95,96} This approach can be difficult to implement and requires large groups of patients and often a long follow-up.

A more recently proposed indirect approach used a pharmacodynamic model to predict the time course of leucopenia from the drug concentration versus

time curve.^{97,98} Such models are a true justification of TDM when they concern clinical end-points such as leucopenia, which is a primary toxicity of many anticancer drugs and is difficult to predict. Contrary to the direct approach, which relates to a specific treatment or schedule, such models could be used with different drugs or schedules. These two approaches are based on the individual pharmacokinetic parameter estimates, so a sparse sampling strategy might render them more readily applicable in clinical practice.

PHARMACOGENETICS

Pharmacogenetics is the science of incorporating information on inherited genetic variability into predicting treatment response. It provides information that allows the clinician to make a determination of appropriateness and risk of drug therapy prior to the initiation of therapy. It also may then have an additional place in selecting drug or dosage alterations during the treatment for a disease process.

A better understanding of pharmacogenetic associations is especially important in cancer chemotherapy, as many chemotherapeutic agents given for cancer are characterized by a narrow therapeutic index.⁹⁹

Polymorphisms in both the individual's genome, as well as the tumor genome, will affect drug response. Drug-related toxicity almost exclusively depends on the genotype of non-tumor tissue. So, inherited polymorphisms will have a key role with respect to toxicity, a crucial dose-limiting factor in most cancer chemotherapy regimens.

Pharmacogenetics aims to use knowledge of these variations to 'tailor' therapy for improved response and reduced toxicity. Most research so far has focused on single polymorphisms. A more comprehensive approach to predict treatment response will be to consider genetic variation in entire biological and pharmacological pathways.

Genetic variations are the result of multiple mechanisms such as single nucleotide polymorphisms (SNPs) (over 90%), insertion, deletion, tandem repeats, and microsatellites. In an attempt to individualize therapy, pharmacogenetics is used in search for answers to the hereditary basis for individual differences in drug response.

Some drugs require metabolism to be activated or inactivated. Some enzymes involved in the biotransformation have polymorphic expression. Therefore,

assessing enzyme activity (ie phenotype) or gene mutations (ie genotype) could help to predict optimal dose regimens.⁹⁹⁻¹⁰¹

Fluorouracil (5-FU) is the most frequent chemotherapy drug used in combination therapy to treat a wide variety of malignancies of the gastrointestinal tract, breast, and head and neck. Eighty to ninety percent of 5-FU dose is catabolized into inactive dihydrofluorouracil (5FUH2) by dihydropyrimidine dehydrogenase (DPD). A genetic polymorphism caused by mutations in the DPD gene results in DPD enzyme with partial to absolute loss of activity. Patients who are genetically deficient in this enzyme are at particular risk of life-threatening toxicity.¹⁰² The gene for DPD has recently been localized to chromosome 1p22, and at least one mutation has been identified.¹⁰³⁻¹⁰⁵ The most frequent mutation in patients with partial or complete DPD deficiency is allele DPD*2A. Patients heterozygous for this polymorphism have low DPD activity and toxicity to 5FU. Family studies in pediatric patients with DPD-deficiency phenotypes and in cancer patients having moderate to severe toxicity after 5-FU treatment show poor genotype-phenotype concordance. It seems that genotyping tests for DPD mutations have low sensitivity in identifying high-risk patients, and as yet no single test has been validated as a tool to individualize 5-FU therapy. Currently, the apparently high false-negative rate for DPD as a predictor for severe 5-FU toxicity restricts the testing of DPD*2A.

On the other hand, the thymidylate-synthase promoter-enhancer region (TSER) polymorphism has been investigated in studies that evaluate response or toxicity from 5-FU treatment. Overall, findings indicate that genotypes that are associated with lower thymidylate-synthase expression confer an increased sensitivity towards 5-FU therapy, although possibly at the expense of greater toxicity. However, most of these studies had limited sample sizes, which needs to be taken into consideration when interpreting the results.¹⁰⁶

Mercaptopurine (MP) is widely used in combination with methotrexate for childhood acute lymphoblastic leukemia (ALL) and in the treatment of Hodgkin disease. As an inactive prodrug, MP must be converted to its active intracellular nucleotide metabolites to exert cytotoxicity. To this point, intracellular thioguanine nucleotides (TGN) serve as the most helpful measure of systemic exposure. Thiopurine S-methyltransferase (TPMT) is a cytosolic enzyme that catalyzes the S-methylation of MP, an inactivation pathway that competes with the activation pathway to TGNs.

Pharmacogenetics causes variability in the metabolism of MP.¹⁰⁷ A polymorphic variation exists in the activity of this enzyme¹⁰⁷⁻¹⁰⁹ with 10% of the population having intermediate activity and 1 in 300 individuals inheriting TPMT deficiency as an autosomal recessive trait. Deficiency in TPMT, owing to homozygosity for low TPMT can lead to marked hematopoietic toxicity if treated with routine doses of MP. TPMT activity varies widely in the subpopulation with intermediate TPMT activity and can be related inversely to formation of the TGN metabolites and therapeutic response. Finally, homozygotes for high TPMT activity may be resistant to MP therapy and can tolerate high doses of the drug, without experiencing myelosuppression because they force more of the drug to the inactivation pathway and less to TGN.

Individualization of MP dose, based on TPMT activity, is a good example of the use of pharmacogenetics to optimize drug therapy. Patients who are TPMT-deficient can be safely and effectively treated with MP if their dosage is reduced. Thus, TPMT is an example of a clinically significant genetic polymorphism where prospective genotyping might allow individualization of drug therapy and thereby maximize efficacy and minimize toxicity. TPMT genotyping or phenotyping is now being used in major centers for dose optimization, in order to reduce the likelihood of adverse drug reaction in children with acute lymphocytic leukemia.¹¹⁰

Many anticancer drugs are extensively metabolized by CYP enzymes, especially the isoenzymes CYP3A4 and CYP2C8. The UDP glycosyltransferases (UGTs) represent a superfamily of enzymes that catalyze addition of the glycosyl group from a nucleotide sugar to a hydrophobic molecule.

Irinotecan, is an anticancer agent used in the treatment of colon cancer, lung, and other solid tumors. Irinotecan is activated by a carboxylesterase to form the active metabolite SN-38, a potent inhibitor of topoisomerase I. SN-38 is further conjugated by UGT specifically the UGT 1A1 isoform.^{111,112} This same isoform conjugates bilirubin or several endogenous substrates. UGT1A1 promoter polymorphisms result in reduced UGT1A1 expression and activity. Reduced UGT1A1 is linked to a high risk (about 4-fold) of severe toxicity from irinotecan treatment, including dose limiting diarrhea and neutropenia. However, UGT1A1 polymorphism is not the sole predictor of irinotecan clearance because of irinotecan complex metabolism and elimination (involving carboxylesterase, CYP3A4, and transporters).¹¹³

A very important deficit in glucuronidation was observed in patients with Gilbert syndrome, suggesting a genetic predisposition to the metabolism of irinotecan and an increased risk of irinotecan toxicity.¹¹⁴ It was suggested that unconjugated serum bilirubin could be a predictive parameter for irinotecan toxicity. Better still is the individualization of irinotecan dose by phenotyping of UGT 1A1 by gene diagnosis.

Most drugs used in cancer chemotherapy are metabolized by CYP3A, CYP1A, CYP2B, and CYP2C isoforms. The most abundant CYP expressed in the liver, accounting for 60% of the CYP activity, and in intestinal wall is CYP3A4. Twenty-five variant alleles for CYP3A4 have been reported to date, however, despite significant inter-individual variation genotype/phenotype studies have not shown concordance in the expression levels and activity. CYP3A5 expression is polymorphic, with readily detectable expression levels in about 30% of livers and low to undetectable levels in the rest.

CYP3A4 is involved in the metabolism of a majority of anticancer drugs, CYP3A5 polymorphisms could affect the pharmacodynamics of agents that are metabolized by both enzymes. CYP3A4 and CYP3A5 catalyze the initial oxidation (before cyclization) of docetaxel, a semisynthetic used in the treatment of breast and ovarian cancers. The contribution of the CYP3A polymorphism to the effect of anticancer drugs has not been elucidated, but because almost half of all anti-cancer drugs are CYP3A substrates, polymorphisms in CYPs are likely to affect the pharmacodynamics of anticancer drugs.¹⁰⁶

FUTURE DEVELOPMENTS

The value of clinical pharmacokinetics must be judged with regard to patient outcomes such as choosing to include the dose-limiting toxicity, taking into account the most important covariates, and selecting the best concentration-effect relationship.

Explorations may be complicated by the fact that the dose-limiting toxicity chosen, is a delayed reaction to the treatment and that toxicity, with efficacy, most often represent cumulated doses and appear only after multiple doses. Identification of at-risk subpopulations such as patients with hepatic or renal impairment would have to be taken into account when defining pharmacokinetic-pharmacodynamic relationships.¹¹⁵

In most cases so far, only the plasma concentration of parent drugs has been taken into account in the evaluation of drug-exposure. However, metabolites can present a dose-limiting toxicity too, and the nature of this toxicity can be slightly different from that of the parent drug. Similarly, drug metabolites can be therapeutically active, and therefore their blood concentration is linked to treatment efficacy (eg irinotecan and its active metabolite or methotrexate and its polyglutamated intracellular metabolites).¹¹⁶ Moreover, the analytical methods used for the TDM of anticancer drugs are largely concerned with total forms, except for platinum compounds, whereas pharmacokinetic parameters derived from plasma concentrations of the unbound forms may be better predictors of severe toxicity and therapeutic response than those derived from total forms.

New analytical methods, such as liquid chromatography combined with mass spectrometry or tandem mass spectrometry, have introduced a key improvement in specificity and sensitivity. They have been used recently for the determination of an increasing number of drugs and active metabolites in plasma or in surrogate tissues.¹¹⁷

They could be employed to routinely assess metabolites at low concentration or unbound active molecules. The development of non-invasive methods for the determination of drugs and active metabolite concentration and/or effects on tumor tissue would help to find more accurate pharmacokinetic-pharmacodynamic relationships and overcome the long lag time between the determination of drug in plasma and assessment of the ultimate pharmacodynamic effects, such as survival time or tumor size change.¹¹⁸ Nuclear magnetic resonance has been used to determine the kinetics of active molecule uptake and retention in solid tumors for fluorouracil.¹¹⁹ Another promising technique that allows determination of effects within tumors is positron emission tomography associated with a scanner.

To date, examples of TDM of anticancer drugs often stem from relationships between serum concentrations (or other exposure variables such as AUC) and toxicity, whereas the relationships with therapeutic effects are not well proven for many cancers and drugs. In the future, a better knowledge of the relationships between pharmacokinetic parameter values or exposure variables and tumor growth or survival rate, for example, will contribute to the improvement of treatment efficacy and patient's outcome by allowing an *a priori* determination of the first dose and a *posteriori* adjustment of the following doses.

There is an increasing focus on the implementation of pharmacokinetic- pharmacodynamic studies and modeling from the beginning of a drug's evaluation.¹²⁰ New chemotherapeutic agents may fail new drug development because of unfavorable pharmacokinetics as well as pharmacodynamics profiles.¹²¹ However, to date, a large number of studies provide kinetic and dynamic data without investigating the relationships between them.¹²² The critical effect of pharmacokinetic monitoring in cancer chemotherapy will depend on the ability to develop pharmacokinetic-pharmacodynamic models that take into account covariates such as disease state, concomitant treatments, pharmacokinetic behavior (eg enzyme induction or inhibition, binding to plasma proteins)¹²³ and other patient-related factors. The data set should be obtained in an ample number of patients, ensuring inclusion of the widest range of the different physiological factors influencing pharmacokinetics and pharmacodynamics, and representation of the target patient population with respect to age, gender, path physiological characteristics, and concurrent and previous treatments. Ideally, studies should be long enough to evaluate survival rates. Otherwise, the search for relevant and useful covariates may not be successful.¹²⁴

Specific and easier to use software, as well as a better knowledge of pharmacokinetic- pharmacodynamic methodology among clinical pharmacist, is required.¹²² Finally, circadian time of infusion should be taken into account for drugs for which recent studies have found that data such as CL, C_{max}, AUC, or protein binding were chronomodulated on a circadian basis. For example for 5-FU a chronomodulated delivery schedule using a perfusion rate inversely proportional to the circadian variations of clearance resulted in an increased effectiveness of the treatment and decreased occurrence of drug-associated side-effects.¹²⁵

Chronotherapy has been shown to be significantly less toxic and more effective than flat infusion. The concept of circadian selectivity of cancer chemotherapy is well founded and easy to implement as programmable pumps for the delivery of chemotherapy are available and they are of manageable size, weight, and cost.¹²⁶

Pharmacokinetic-pharmacodynamic modeling generally attempts to study models for a single drug, and multi-drug regimens have had little attention, although the coupled treatments can be retained as covariates in the final population model. The coupled drugs usually have different mechanisms of action

and toxicity profile, although in some cases a drug is administered to enhance the effects of another. In such cases, an alternative approach to TDM that combines pharmacokinetic and pharmacodynamic monitoring has been proposed.¹²⁷ ALL treatment protocols based on combination chemotherapy were used as a model. Different pharmacodynamic endpoints, such as the initial reduction of leukemia cells in peripheral blood or in bone marrow and the detection of minimal residual disease by immunological or polymerase chain reaction-based methods were observed to identify those who exhibited poor response to therapy. Systemic exposure was measured to determine whether poor response could result from too low an exposure to individual drugs. If systemic exposure appeared optimal, then alternative drug therapy or different treatment strategies might be tried. Ideally, a true global strategy would have required studies on pharmacodynamic interactions (eg synergy, additively, antagonism) on therapeutic as well as toxic effects, and translated them as interaction terms in the model.

MULTIDISCIPLINARY APPROACH OF TDM IN ANTICANCER DRUGS

Establishing a relationship between drug concentration and drug effect is an essential foundation for use of TDM with the ultimate goal of optimizing cancer chemotherapy.

As progress continues in this field, the justification for TDM will become gradually more convincing for selected antineoplastic agents. However, implementation of TDM requires more than just a defined therapeutic range for specific agents, it will also require a well-coordinated multidisciplinary effort. The appropriate application requires the correct administration of drug, correct collection and processing of blood samples, precise and accurate measurement of drug or active metabolites, and appropriate interpretation of results.³ The whole process involves the skill and knowledge of different professionals, including pharmacists, nurses, phlebotomists, technicians/technologists, clinical chemists, clinical pharmacists, pharmacokinetics, and physicians. Each person involved in the process must clearly understand the limitations and difficulties of TDM and make efforts to fully optimize TDM at each step; failure at any step can compromise the whole process.

THE ROLE OF CLINICAL PHARMACIST

The primary clinician chooses the initial dosing regimen for the patient and makes subsequent changes of dosage depending on clinical response, TDM, and other clinical or biochemical parameters. Hence, enough knowledge in pharmacokinetics and pharmacodynamics must be acquired to appreciate the potential and the limitations of TDM, and the sources and consequences of errors that can occur during the TDM process. Clinicians must carefully interpret results of drug concentrations, recognizing that drug measurements are only an intermediate endpoint, with clinical response being the ultimate measure of therapeutic outcome.

Well-designed clinical studies are essential to define the pharmacokinetics of medications and accurately define a therapeutic range for TDM. One of the essential roles of the science of pharmacokinetics is to construct, evaluate, and select a mathematically correct and a physiologically appropriate model for determination of pharmacokinetic parameters. The critical analysis of these parameters is essential because this determines the accuracy of the calculated pharmacokinetic parameters^{128,129} and subsequent dosage adjustments to achieve the target drug concentration. It is critical to select the appropriate pharmacodynamic models for establishing strong concentration–effect relationships, which can eventually provide the foundation for establishing ‘therapeutic ranges’ for TDM.

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