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Review

Review of therapeutic drug monitoring of anticancer drugs part 1 – Cytotoxics ☆

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Abstract Most anticancer drugs are characterised by a steep dose–response relationship and narrow therapeutic window. Inter-individual pharmacokinetic (PK) variability is often substantial. The most relevant PK parameter for cytotoxic drugs is the area under the plasma concentration versus time curve (AUC). Thus it is somewhat surprising that therapeutic drug monitoring (TDM) is still uncommon for the majority of agents. Goals of the review were to assess the rationale for more widely used TDM of cytotoxics in oncology. There are several reasons why TDM has never been fully implemented into daily oncology practice. These include difficulties in establishing appropriate concentration target ranges, common use of combination chemotherapies for many tumour types, analytical challenges with prodrugs, intracellular compounds, the paucity of published data from pharmacological trials and 'Day1 = Day21' administration schedules. There are some specific situations for which these limitations are overcome, including high dose methotrexate, 5-fluorouracil infusion, mitotane and some high dose chemotherapy regimens. TDM in paediatric oncology represents an important challenge. Established TDM approaches includes the widely used anticancer agents carboplatin, busulfan and methotrexate, with 13-cis-retinoic acid also recently of interest.

☆ This review is the result of a workshop carried out under the auspices of the French Society of Oncology Pharmacy (SFPO). It has been elaborated with the participation of different European experts (authors) in anticancer drugs therapeutic drug monitoring.

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Considerable effort should be made to better define concentration–effect relationships and to utilise tools such as population PK/PD models and comparative randomised trials of classic dosing versus pharmacokinetically guided adaptive dosing. There is an important heterogeneity among clinical practices and a strong need to promote TDM guidelines among the oncological community.

1. Rationale for therapeutic drug monitoring (TDM)

Cytotoxic anticancer drugs fit many of the criteria commonly defined as prerequisites for utilising TDM approaches. Firstly, the extent of inter-individual pharmacokinetic (PK) variability exhibited is large in the majority of cases. It is commonplace to observe coefficients of variation of clearance of more than 50% for these drugs. Moreover, this level of variation is frequently observed when clearance values are expressed per m^2 ($L/h/m^2$), as well as when expressed in L/h, indicating that clearance is poorly correlated with body surface area. This large inter-individual PK variability is likely to be related to genetic differences as well as variations in the functional status of the cancer patients. Secondly, relationships have been described between plasma concentrations and pharmacodynamic (PD) end-points such as percentage decrease in neutrophil counts between pretreatment and nadir values. The most relevant PK parameter for cytotoxic drugs is the area under the plasma concentration versus time curve (AUC). For most cytotoxics AUC is better correlated to PD end-points than specific concentrations, such as the maximum plasma concentration at the end of intravenous infusion or the residual concentration (which is effectively zero since the half-life is negligible with regards to the 3-week interval period between cycles). The third prerequisite of TDM (i.e. a delay between the PD end-point and the time of measurement of plasma concentrations) is fulfilled since the AUC corresponds commonly to one or two days following a short intravenous infusion, with neutrophil and platelet nadir values observed 1–2 weeks after chemotherapy. This administration schedule allows us to understand why TDM is not routinely performed for cytotoxics, as the AUC from a specific patient is obtained after completion of drug administration. Even in the case of the observed AUC value differing significantly from the target AUC, no dose modification can be performed since the drug has already been administered. However, dose individualisation may be considered for treatment cycle 2 based on PK parameters obtained from cycle 1. In routine practice, dose decreases are generally only performed in the case of unacceptable dose limiting toxicity observed between cycles, whereas TDM may provide valuable additional information to guide dose modifications in either direction on subsequent courses of treatment. However, this approach has not been established in general practice for several reasons. As chemotherapy regimens are commonly based on combinations of drugs, determination of AUC values for specific drugs requires multiple blood samples to be taken; PK–PD relationships are more difficult to model for drug combinations and target AUC values for specific drugs are more difficult to define. Other factors include the cost of TDM and the fact that prospective validation of TDM approaches based on randomised studies are challenging to perform. Furthermore, attention must be paid to the results of the studies and the applicability of the strategies in clinical practice [1]. However, there are some specific situations for which these limitations are overcome.

2. TDM and pharmacogenetics

Genetic factors contribute to the phenotype of drug response, but the translation of pharmacogenetic outcomes into clinical practice has proved to be surprisingly disappointing, with relatively few exceptions (e.g. 5-fluorouracil (5-FU), irinotecan, mercaptopurine). A significant proportion of variability in drug response can be attributed to genetic factors through modulation of drug PKs and/or PDs. Therefore, the rationale behind pharmacogenetic studies is to investigate genes encoding drug transporters, drug-metabolising enzymes and drug targets that can predict the usefulness of a particular drug so as to increase the number of responders and decrease the number of subjects affected by adverse drug reactions. Nevertheless, the sources of variability in drug response are multifactorial and apart from genetics, factors such as pathophysiology, environment, diet, drug–drug interactions, drug allergies, medication errors and poor compliance, may all have a profound impact on PKs and/or PDs, thereby affecting therapeutic outcome. Finally, there are many gaps in our current knowledge that limit the application of pharmacogenetic information [2,3].

It is not the goal of this article to discuss the implementation of pharmacogenetics in drug monitoring or to compare the two approaches. Indeed, we would ideally carry out prospective controlled clinical trials to compare the potential benefits of the different approaches. The combined use of classical TDM (as a phenotyping approach) and genotyping of drug metabolic capacity, is currently considered to be the most sophisticated way to individualise the dosage of several