Identifying Sources of Interindividual Pharmacokinetic Variability with Population Modeling

Commentary on Joerger et al., p. 2150

Alex Sparreboom and William D. Figg

Napoleon Bonaparte (1769-1821) once remarked that "medicine is a collection of uncertain prescriptions, the results of which, taken collectively, are more fatal than useful to mankind." Although this needs to be read in historic context, it is still true that, in most common cancer types, many of the currently available drugs have rather limited efficacy combined with a significant degree of toxicity. The major reasons for this have presumably been the lack of detailed knowledge in tumor cell biology and inappropriate preclinical models for the identification and testing of compounds. Moreover, the standard strategy still in use for dose selection of cytotoxic anticancer drugs is to establish a therapeutic dose in phase II trials and subsequently, at best, only modify it for individual differences in body-surface area. There is wealth of experimental data, however, indicating that both the efficacy and the safety of cytotoxic chemotherapeutic treatment might be optimized if dosing strategies would consider individual patient characteristics as they relate to the pharmacokinetic (e.g., measures of liver function), pharmacodynamic (e.g., timing and extent of neutropenia after dosing), or pharmacogenetic profiles of the agent (1). These individual patient characteristics could, depending on the extent of unexplainable drug variability, be characterized following the first dose of the drug and subsequent blood sampling.

The study of population pharmacokinetics seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these alterations so that, if these are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified in the individual patient. It is obvious that a careful collection of data during the development of drugs and subsequent analyses could be helpful to collect some essential information on the drug. Unfortunately, important information is often lost by failing to analyze this data or due to the fact that the relevant samples or data were never collected.

Historically, this has resulted in the notion that tools for the identification of patient population subgroups are inadequate for most of the currently approved anticancer drugs (2).

In the present issue of the Clinical Cancer Research, Joerger et al. describe the first comprehensive and long overdue population pharmacokinetic modeling analysis for paclitaxel (3), more than two decades after the clinical development of the drug was initiated. The authors are to be congratulated for meticulously collecting blood samples on 168 patients treated with paclitaxel over the last 15 years and for planning and executing this retrospective investigation. Using complex nonlinear mixed-effect modeling algorithms, the authors showed that among the variables evaluated sex, body-surface area, age, and serum bilirubin all independently and significantly correlated with the disposition and elimination pathways of paclitaxel. As pointed out by Joerger et al., similar associations between body-surface area, age, and bilirubin and the pharmacokinetic profile of paclitaxel were reported previously in smaller studies and are now confirmed. Of particular interest is the authors' novel finding that male gender was positively correlated with the maximum elimination capacity of paclitaxel, adding to a growing body of evidence that the pharmacokinetic profile of various anticancer drugs exhibits significant sexual dimorphism (4).

A few issues need to be considered to appraise the authors' final conclusion that future utilization of their pharmacokinetic model may include prospective covariate-adapted paclitaxel dosing to lower interindividual variability of drug exposure and toxicity. First, the development of rational dose individualization strategies depends, with respect to pharmacokinetics, on choosing an adequate matrix to measure (e.g., blood, plasma, and plasma water), an adequate analyte to monitor (parent drug or metabolites), and an adequate way of summarizing exposure-effect relationships (e.g., area under the curve or time above a threshold concentration). It is further necessary that exposure is quantitatively linked to the effect and/or toxicity possibly through a suitable biomarker. Unfortunately, in the study by Joerger et al., efficacy and toxicity data were not considered because the data were obtained from patients treated with variable doses of paclitaxel, either given alone or in combination with other agents, and in a variety of diseases. The authors focused in their population analysis on finding predictors of the duration that concentrations of paclitaxel in plasma are >0.1 μmol/L, which variable is associated with the main side effect of paclitaxel, neutropenia, and overall survival in non–small cell lung cancer. It is noteworthy though that the use and generalizability of this
empirically designed threshold model to describe pharmacokinetic-pharmacodynamic relationships for paclitaxel is somewhat controversial and that various alternative models have been proposed (5). In any event, the lack of a solid foundation based on pharmacodynamic data makes it unclear if the current findings by Joerger et al. already provide meaningful tools for medical decision-making in clinical practice. For example, body-surface area was found to be associated with paclitaxel elimination, as predicted previously, but flat-fixed dosing strategies have already been shown to be feasible (6, 7), although these studies were not randomized and hence a direct comparison with dose calculations based on body size cannot be made. It is of note that the identification of body-surface area in a population pharmacokinetic model as a significant covariate, with subsequent demonstration of the clinical feasibility of delivering a fixed dose independent of body-size measures, has also been documented recently for the anticancer drug cisplatin (8, 9).

The described relationship between sex and paclitaxel pharmacokinetics by Joerger et al. is theoretically plausible, as paclitaxel undergoes substantial fecal excretion in humans preceded by biliary and intestinal secretion, which pathways are likely mediated, at least in part, by the ATP-binding cassette transporter, ABCB1 (MDR1; P-glycoprotein; ref. 10). In contrast to expression of the main enzymes involved in paclitaxel metabolism in humans (i.e., CYP2C8, CYP3A4, and CYP3A5), and where sex dependence in humans has not been firmly established (11), ABCB1 expression is >2-fold lower in females compared with males (12). It has been speculated previously that this differential expression is contributing to the fact that women experience more myelosuppression than men following chemotherapeutic treatment with ABCB1 substrates (13, 14). However, to the best of our knowledge, this has not yet been reported for paclitaxel and clearly deserves further study.

Finally, it should be pointed out that finding a statistically significant correlation between a given demographic characteristic and paclitaxel elimination in a population pharmacokinetic model does not necessarily guarantee that a clinically meaningful relationship exists. As outlined by Joerger et al., the percent reduction in the interindividual variability of the studied pharmacokinetic variables after consideration of all significant covariates simultaneously was relatively modest. Hence, sex, body-surface area, age, and serum bilirubin combined accounted for only a minority of the total interindividual variability in paclitaxel pharmacokinetics and do not provide quantitative predictability in this particular patient population. This suggests that the ability to select more homogenous populations (beyond consideration of simple clinical factors) and predict toxicity and response remains a major challenge for paclitaxel and the further development of pharmacogenetics could potentially help in this respect. Nonetheless, two recent preliminary analyses indicate that, in general Asian and Caucasian populations, the contribution of common genetic variants in the CYP2C8, CYP3A4, CYP3A5, and ABCB1 genes to explaining residual pharmacokinetic variability of paclitaxel is limited at best (15, 16). However, the potential usefulness of pharmacogenetic approaches to individualizing treatment with paclitaxel has not been studied exhaustively. For example, the number of genes implicated in the agent’s disposition has been growing in recent years and now also include the hepatocellular uptake transporters SLCO1B3 (OATP1B3, OATP8; ref. 17), and SLC22A7 (OAT2; ref. 18), and ATP-binding cassette transporters ABCCC2 (cMOAT, MRP2; ref. 19), ABCBC10 (MRP7; ref. 20), and potentially also ABCB4 (MDR3; ref. 21) and ABCB11 (sister of P-glycoprotein, bile salt export pump; ref. 22). Prospective studies are urgently needed to search for relationships between toxicity/response and polymorphisms in the enzymes and transporters involved in the pharmacokinetics and pharmacodynamics of paclitaxel. Such studies using pharmacogenetic strategies, possibly in conjunction with the use of surrogate probe drugs to determine individual enzyme and transporter activity a priori, are of great interest and may identify inherited causes of interindividual pharmacologic variability and eventually result in a major advance in the individualized use of taxanes.

The described population pharmacokinetic model by Joerger et al. has further and significantly enhanced our understanding of the complex interactions of biological and physiologic variables that affect the pharmacokinetic profile of paclitaxel. Furthermore, the model provides the basis for designing future, prospective investigations aimed at refining the model and for evaluating alternative and improved dosing regimens for this clinically important drug.

References

polymorphisms of CYP2C8, CYP3A4, and MDR1.


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