Need and Potential for Predictive Tests of Hepatic Metabolism of Anticancer Drugs

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“All science is concerned with the relationship of cause and effect. Each scientific discovery increases man’s ability to predict the consequences of his actions and thus his ability to control future events.”

Lawrence J. Peters 1925–1990

Numerous studies have documented extensive interpatient variability in systemic clearance of many anticancer drugs. For any given drug dosage, this variability translates into highly variable drug systemic exposure. This is a clinically relevant problem because anticancer drugs have a narrow therapeutic index (i.e., ratio of drug exposures associated with antitumor effect and unacceptable toxicity). Thus, efforts have been made to find approaches to minimize this wide interpatient variability in drug disposition. For anticancer drugs that are eliminated by the kidney (e.g., carboplatin), indirect measures of renal function (i.e., glomerular filtration) have been related to drug clearance. This relationship has been used to guide initial drug dosage and presumably decrease interpatient variability in systemic exposure. However, many of the commonly used anticancer drugs undergo, at least in part, hepatic metabolism, and for those drugs no measure of hepatic function has been found to be universally predictive of hepatic drug clearance.

Out of this need to quantitate the interpatient variability in hepatic drug metabolism has arisen the development of model substrates or in vivo probe assays of hepatic metabolizing activity. With this model drug approach one would predict that a particular patient’s ability to eliminate a prototypic drug would correlate with that patient’s ability to eliminate many other drugs. If this approach were feasible, many applications are obvious. Patients could be phenotyped before they received the drug of interest, which would reduce the likelihood of toxicity or undertreatment that is often associated with wide interpatient variability. Moreover, the results of the phenotyping studies could apply to more than just one drug. Finally, phenotyping the patient over time could assess changes induced environmentally in hepatic drug metabolism occurring in the same patient during a course of the disease. Numerous single agents have been proposed as model substrates, including antipyrine, midazolam, and lorazepam, as well as cocktails of multiple agents, including lorazepam-indocyanine green-antipyrine, antipyrine-theophylline, and antipyrine-nifedipine-mephenytoin-sparteine. However, each one of these substrates has had limitations (reviewed in Ref. 1).

Considerable work has been devoted to designing a specific in vivo probe of hepatic CYP3A4 activity because this is the dominant hepatic and intestinal CYP and is involved in the metabolism of many medications than any other drug-metabolizing enzyme. Moreover, considerable interindividual variation has been reported in metabolism of many CYP3A4 substrates. This may translate into either subtherapeutic or toxic effects in individuals given standard doses of CYP3A4 substrates, particularly those with narrow therapeutic indices, such as immunosuppressants (e.g., cyclosporine A) and many anticancer drugs (e.g., vinblastine and etoposide), that are metabolized by CYP3A4.

Pharmacogenetic molecular diagnostics are reasonable approaches for dosing of some anticancer drugs, such as 6-mercaptopurine (2). However, except in patients who inherit a complete deficiency of a drug-metabolizing enzyme, this approach may not be as useful as tests that determine the phenotype of a cancer patient because of the potential for confounding factors such as disease, drugs, and nutrition. For example, genotype would not be useful in the patient with massive hepatic metastasis or in the patient taking a potent inducer or inhibitor of CYP3A.

An ideal phenotyping test would be safe, quick to perform with same-day results, and should be highly predictive of the disposition of the drug(s) of interest. It is impractical to use either nontherapeutic doses of anticancer drugs or model substrates because of analytical hurdles, delays in analysis, and the need for repetitive blood sampling from patients who are frequently anemic. The ERMBT has been the accepted “gold standard” to phenotype hepatic CYP3A4 activity and is the most extensively characterized CYP3A4 bioassay in humans. This assay is based on the fact that CYP3A4 demethylates [14C]N-methyl erythromycin, and the 14C in the methyl group appears in the breath as 14CO2. The test is safe, easy, and relatively quick to administer; the results can be available within hours, and the test is commercially available (Metabolic Solutions, Inc., Nashua, NH). The ERMBT has been widely used in drug development and numerous clinical studies and is a good predictor of the appropriate stable daily dose of cyclosporine (3). Most recently Hirth et al. (4) have suggested it may be clinically useful in dosing CYP3A4 substrates, such as the cancer chemotherapy docetaxel.

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2 The abbreviations used are: CYP, cytochrome; ERMBT, erythromycin breath test; Pgp, P-glycoprotein.
However, the ERMBT has not always correlated well with other probe assays of CYP3A, including midazolam clearance (5), raising the question about what the ERMBT result is actually measuring. The report by Rivory et al. (6) in this issue of Clinical Cancer Research sets out to optimize the ERMBT in an effort to ultimately guide dosing of anticancer drugs. The rather surprising observation was that the ERMBT results, as conventionally expressed, did not correlate well with the systemic clearance of erythromycin. On the basis of our work demonstrating that erythromycin is a substrate for the human MDR1/ P-glycoprotein (Pgp) drug efflux transporter (7), this discordance is probably because Pgp is a major determinant of erythromycin clearance and seems likely to also influence breath $^{14}$CO$_2$ production. Indeed, we have demonstrated recently that the ERMBT measures both hepatic CYP3A and Pgp (8). This may give the ERMBT an advantage over other probes assays because many CYP3A4 substrates, particularly anticancer drugs, are also Pgp substrates. The novel methods used by Rivory et al. (6) to express the results of the ERMBT (e.g., $1/T_{MAX}$ and $CER_{3\text{ min}}/CER_{MAX}$) may be useful in situations where the relevant molecular determinants of disposition of a given anticancer drug are exactly the same as erythromycin. However, the relative importance of CYP3A4 or Pgp to the disposition of any drug will vary, depending on the dose of the drug and the kinetics of interaction with these two proteins. Thus, more work clearly is needed, and creative analyses of the breath CO$_2$ production, such as the current study, should be encouraged. Indeed, it remains a possibility that a simultaneous measure of blood erythromycin coupled with the ERMBT will allow for the combined assessment of both hepatic CYP3A4 and Pgp (8).

Thus, in the future, once we are able to predict the activity of CYP3A4 and Pgp, we will be faced with the issue of how to “control future events.” To phrase this differently, once we can account for the interpatient variability by accurately predicting hepatic CYP3A4 activity, then the question becomes what level of systemic exposure is associated with the least toxicity and most antitumor response. If we indeed can account for interpatient variability, we then need to know where to target drug dosing, and this will require well-designed clinical trials with the goal to define the therapeutic index for the drug of interest, both as a single agent and in combinations. Anticancer drugs provide an excellent example of a class of drugs in need of an approach to reducing interpatient variability in drug systemic exposure. The results of Rivory et al. (6) with the ERMBT show potential and are worthy of more research.

References
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