Cytochrome P-450 and Other Determinants of Pharmacokinetics, Toxicity, and Efficacy in Humans

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In this issue of Clinical Cancer Research, Hirth et al. (1) describe the use of the ERMBT (2) as a probe for drug metabolism and its potential use for individualizing doses of docetaxel. Because of the narrow therapeutic index for anticancer drugs, oncologists have a long-standing tradition of monitoring and adjusting doses for specific patients. Docetaxel is an excellent candidate for individualization because it is metabolized primarily by CYP3A, an enzyme that is known to have large interindividual variability.

For most agents, there are dose reduction schemes for patients who experience toxicity at standard doses. When risk factors are known in advance, e.g., extensive prior treatment with cytotoxic drugs or elevations in liver enzyme tests, even the initial dose may be reduced. Although docetaxel administration is already guided by liver enzyme tests, the two patients who developed severe toxicity in the study of Hirth et al. (1) were not identified by these tests.

Unlike drugs for other diseases, doses for anticancer therapeutics are routinely adjusted on the basis of body surface area. However, interpatient variability is not noticeably reduced (2). Thus, alternate approaches such as the ERMBT are required and are being explored.

Relationships among CYP Metabolism, Systemic Exposure, and Clinical End Points

Both toxicity and efficacy are determined, in part, by the circulating concentrations of drug. Metabolism is the principal determinant of circulating concentrations, and the CYP family provides the most common catabolic machinery (3). The article by Hirth et al. (1) focuses our attention on ways to adjust doses based on measures of interpatient variability in metabolism. The goal is to determine relationships between clinical end points (toxicity and/or efficacy) and a measure of exposure to the drug (PK). On a routine basis, it is unrealistic to expect a series of blood samples to be obtained for a PK study in each patient. Furthermore, unless a test dose of drug is used before therapy (4), it is too late to adjust for the first cycle after the standard dose has already been given.

The ERMBT has multiple advantages: it is rapid, relatively noninvasive, requires only a single time point, and can be used prospectively before dosing. The ERMBT has been used in drug development for therapeutic disciplines outside oncology. It builds on a tradition of more than 25 years of searching for breath tests or similar markers of drug exposure. Initially, a single probe, such as [14C]CO₂ elimination after a dose of [14C]aminopyrine (5), was thought to provide a universal indicator of hepatic oxidative functioning. The ERMBT represents a second generation of probes that recognizes that each metabolic pathway can vary independently and must be probed separately. Thus, ERMBT was developed only for drugs metabolized via CYP3A, such as docetaxel. Similar [14C]CO₂ breath tests have also been reported for CYP1A2 (6) and CYP2E1 (7).

Because of the interplay of metabolism with transport systems such as P-glycoprotein, it is possible that more than one probe will be needed for CYP3A. Thus, it has been reported that the ERMBT does not correlate with the kinetics of midazolam, which is not a substrate for transporters but is another common probe for CYP3A (8). Hirth et al. (1) note that their study was small; therefore, it is encouraging that they report that a larger study is under way, as well as additional plans for customized dosing. Even if it is confirmed that ERMBT is an excellent probe for docetaxel, separate studies would be required to validate the use of ERMBT for other drugs, such as etoposide, which are also substrates for transporters and metabolized by CYP3A.

Hirth et al. studied single-agent docetaxel. Taxanes are now widely used in combination with other drugs, such as anthracyclines. Many of these drugs are also myelotoxic, and Hirth et al. (1) comment that the ERMBT could help sort out the specific contribution of docetaxel from that of other drugs that are not CYP3A4 mediated.

Other Elimination Pathways

There are many drug-metabolizing enzymes outside the CYP family. Ratain et al. (9) demonstrated the ability to adjust doses of amonafide, based on caffeine as a phenotypic probe for N-acetyltransferase. This group also demonstrated that the toxicity of irinotecan was related to expression of glucuronosyltransferase (10) and suggested dose adjustments based on genotyping for the specific enzyme.

Because of the narrow therapeutic range of anticancer drugs, lowering the likelihood of toxicity in the patients at greatest risk is a useful contribution. Unfortunately, we have spent less time focusing on patients with high rates of drug removal from the body. These patients face an increased risk of drug failure. Evans et al. (11) specifically targeted this group of patients and adjusted doses during therapy, with improved efficacy. Of the three drugs adjusted (methotrexate, teniposide, and cytarabine), only teniposide is metabolized by CYP.

Milano et al. (12) conducted a similar study for 5-fluorouracil, which is metabolized by dihydropyrimidine dehydrogen-
ase, a non-CYP enzyme. They reported that toxicity can be reduced and efficacy can be improved by adjusting doses based on plasma levels measured during therapy.

In view of the usually dominant role for metabolism, it is somewhat ironic that individualized care of oncology patients was first established for methotrexate, a drug that is largely excreted in the urine (13). Today, the most established practice for the adjustment of doses is for carboplatin, a drug that is also primarily excreted unchanged in the urine (14, 15). Carboplatin adjustment has the advantage of using a clinical chemistry parameter already available for all patients. Unfortunately, whereas creatinine clearance has been repeatedly demonstrated to be a worthwhile surrogate for renal clearance of many drugs that are filtered, no similar index has been found for any drug-metabolizing enzymes.

Beyond Systemic Exposure

The ERMBT and other techniques discussed thus far illustrate ways to optimize delivery to the tumor by balancing delivery and elimination rates, subject to the constraints of toxicity. Unfortunately, none of these procedures address variations in the intrinsic sensitivity of the tumor to a particular drug, which is likely to be a larger factor. For example, differences in expression of transporters are strongly related to tumor sensitivity to taxanes. However, plasma levels of taxanes do not reflect individual variations in tumor transport.

When intracellular concentrations can be obtained, particularly for an activated form of the drug, individualized therapy can be based on events occurring at the target site. This principle has been elegantly demonstrated for leukemia by the work of Gandhi et al. (16) but is much more difficult for solid tumors.

Concluding Comments

As we enter an era in which the molecular signature of tumors will be increasingly available, we need to remember that antitumor therapy must be guided by the characteristics of the host as well as the tumor. Tumor parameters can guide selection of the most appropriate drug, but we still need to know host factors such as drug metabolism to get the dose right.

There is substantial overlap in the conceptual approaches and working tools that define both the tumor and the host. When available, genotyping of tumors can provide therapeutic insights beyond the conventional, histopathological-oriented approach. DNA of the host is readily available from peripheral blood cells, and genotyping of the host has already demonstrated utility in pilot studies for selecting doses of drugs as diverse as mercaptopurine, fluorouracil, irinotecan, and amonafide.

The ERMBT study of Hirth et al. (1) provides a useful framework for understanding noninvasive, phenotypic approaches to dosage individualization based on host factors. An analogous approach for noninvasive phenotyping of inaccessible tumors has not yet emerged fully, although functional imaging techniques are a very promising approach.

References


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