

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Effects of Organ Dysfunction on Drug Dosing

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H&O What are the important concepts to consider when administering a drug to a patient?

ME There are two important concepts to consider. The first, pharmacokinetics, addresses the effect of the body on a drug, such as the rates of absorption if taken by mouth, metabolism of the drug, distribution to tissues, and excretion. The second concept, pharmacodynamics, examines the effect of a drug on the body. Ideally, the effect of the drug should be beneficial. With anticancer agents, it is also expected that the drug will be associated with some toxic effect on the body and that this effect is necessary in order to also achieve the beneficial effects. The dose of a drug that causes significant damage to a patient divided by the dose required to produce the therapeutic response is known as the therapeutic index. With most anticancer agents, this index is relatively low, in the range of 1.5–2.

H&O How does organ dysfunction affect pharmacokinetics and pharmacodynamics?

ME Organ dysfunction can increase exposure to a drug, resulting in potentially greater benefit but also potentially greater toxicity without increasing the dose. This increased exposure may result from changes in the way a drug is metabolized or excreted in individuals with organ dysfunction compared to those with normal organ function.

H&O How is organ dysfunction defined?

ME The two organs most likely to be involved in these processes are the liver and kidneys. In general, eligibility requirements for clinical trials of anticancer agents define acceptable kidney function as a creatinine clearance greater than 60 mL/min, although for drugs dosed on the basis of body surface area, this threshold should in

theory be normalized to an average body surface area of 1.73 m². Normal renal function, as defined by the US Food and Drug Administration (FDA), is actually slightly higher, greater than 80 mL/min per 1.73 m². Therefore many patients enrolled in studies of anticancer agents already have what the FDA classifies as mildly impaired kidney function.

The currently available liver function tests (LFTs) include bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase. Bilirubin may provide a reasonable reflection of the rate at which a drug is being excreted (or glucuronidated by UGT1A1), but the other measurements are generally not accurate predictors of drug metabolizing capability. Both the Cancer and Leukemia Group B (CALGB) and the National Cancer Institute's Organ Dysfunction Working Group have undertaken the task of defining appropriate dosing for patients with metabolic and excretory organ dysfunction.

H&O How is this issue studied in the process of drug development? How does one know which drugs should undergo dose-reduction studies?

ME Since only a small fraction of new drugs studied in humans are eventually approved for licensing, it is probably illogical to study the effects of organ dysfunction on a drug dose during initial phase I or II clinical trials. It would not be productive to take the time to determine the appropriate dose of a drug that will not be approved for use. Thus, for many drugs that are approved, there is a period of time during which appropriate dosing recommendations are not known. This situation exists even though the primary route of metabolism or excretion of each drug that enters clinical studies is known from in vitro preclinical studies with human hepatocytes and/or cloned enzymes and in vivo animal studies.

The FDA has guidelines for which types of drugs should undergo dose-reduction studies. Currently, these guidelines state that if 10% or less of a drug is excreted in the urine, a prospective study in patients with kidney disease is not required. However, an increasing body of evidence indicates that chronic renal disease results in alteration of hepatic drug metabolizing capability, which may lead to a change in these guidelines.

Another consideration regarding dose-reduction studies is best illustrated by the agent carboplatin. The clearance of this drug is closely tied to kidney function, and dosing schemes have been developed so that patients with varying degrees of renal function receive appropriate exposure to the drug. However, even though a patient with a clinically significant hepatic dysfunction would not be expected to require dose reduction with carboplatin, it is still important to conduct studies to verify this approach. A practicing physician needs to be assured that a patient with a bilirubin of 6 and elevated LFTs, for example, can be given carboplatin safely.

Paclitaxel is primarily metabolized and excreted hepatically. Parallel to the considerations regarding carboplatin, it was equally important to evaluate paclitaxel in patients on dialysis or with severe renal dysfunction, in order to be assured that the pharmacokinetics in this patient subgroup are the same as in patients with normal renal function. The pharmacodynamic consequences of myelosuppression have been shown to be no worse among patients with renal dysfunction than among patients with normal renal function. For both carboplatin and paclitaxel, it is important to conduct prospective studies to determine appropriate dosing schemes.

H&O Is it difficult to conduct such studies?

ME The process of evaluating dose reduction needs can be slow, generally taking at least a year to conduct. No single institution sees enough patients with these degrees of organ dysfunction, and therefore dose-reduction studies are commonly done as multicenter endeavors. In addition, many patients with organ dysfunction have very advanced disease, and thus these studies often have a high percentage of patients who are not fully evaluable for toxicity.

Implicit in these studies is the understanding that drug exposure is in some way related to toxicity. Intensive pharmacokinetic sampling is required, along with the usual careful clinical data collection that is part of any phase I trial. Dose-reduction studies are generally done as a series of independent phase I studies, each with a cohort of patients of a specific subgroup, such as acceptable organ function, mild organ dysfunction, moderate organ dysfunction, and severe organ dysfunction. The dose is then escalated individually for each cohort. Patients with mild dysfunction are often started at the same dose as those with acceptable function because significant perturbation in pharmacokinetics or pharmacodynamics is not expected among patients with mild organ dysfunction. However, patients with moderate organ dysfunction will begin the study at a lower dose than that previously defined as the recommended dose with a gradual escalation to that recommended dose, if it can be tolerated. The

severe-dysfunction cohort is started at an even lower dose. In order to accurately assess the dosing for these various subgroups, experience has shown that it is necessary to have approximately 50–60 patients.

Although historically these studies have focused on defining the appropriate dose for each organ dysfunction subgroup, an alternative approach recently used by CALGB for sorafenib (Nexavar, Bayer/Onyx) focused on defining the pharmacokinetics of this agent in a patient population rather than individual subgroups. The advantage of this approach is that all patients can receive a single standard dose of the drug, followed by intensive pharmacokinetic sampling. Using this design, very few patients are unevaluable for the primary pharmacokinetic endpoint, although less information is obtained regarding toxicity, requiring that dosing recommendations be based primarily on the pharmacokinetic data.

H&O Even if the pharmacokinetics are not altered in a patient with organ dysfunction, is it possible that problems may still arise?

ME Yes. Even if there are no pharmacokinetic alterations, individuals with liver or kidney disease may still have an increased sensitivity to a particular drug. In an individual with low serum albumin, there may be a higher free fraction of the drug, resulting in more myelosuppression, neurotoxicity, or whatever the dose-limiting toxicity of the particular agent might be. Individuals with renal dysfunction may experience increased anemia and have less bone marrow reserve. What would be acceptable drug exposure in a normal patient could cause damage in a patient with underlying liver or kidney disease.

H&O You mentioned that the current LFTs are not very useful. Are new tests being investigated?

ME One alternative approach is to sample the metabolism of a surrogate drug. For most drugs that enter clinical studies, the metabolic pathway has been evaluated beforehand in vitro. Since the majority of agents for treating cancer are metabolized by cytochrome P450 3A4, many investigators use midazolam as a surrogate. Patients are given a low dose, and the amount of time needed for the drug to be metabolized is measured. This method is cumbersome in that it requires an extra day of treatment, drawing blood, and admitting patients to the hospital. This approach is also expensive, requiring six samples to be drawn at approximately \$60 per sample.

An alternative approach is the ¹⁴carbon erythromycin breath test. With this method, patients receive an intravenous injection of ¹⁴carbon-labeled erythromycin, which is then metabolized. The ¹⁴carbon label is liberated as carbon dioxide, and patients are instructed to exhale into a bal-

loon that is coated with a material that traps the carbon dioxide. The radioactivity present in the balloon is then measured. This approach has been shown to correlate with docetaxel clearance, which is related to the degree of myelosuppression that a patient may develop. However, this test is also expensive and its usefulness varies according to how well it is conducted. For example, a patient may not breathe into the balloon as instructed or as desired. The point has been made that multiple balloon samples may be more accurate than a single balloon, but if multiple samples are taken, the time requirement and expense involved may approach that of midazolam sampling.

Both these approaches carry logistical and financial issues that prevent their wide acceptance. However, the standard LFTs are a poor reflection of drug-metabolizing capability, and therefore other approaches must be explored.

H&O In terms of drug dosing, what are the differences between individuals with liver dysfunction and individuals with kidney dysfunction?

ME Patients with kidney dysfunction are often relatively stable, and consequently studies of patients with kidney dysfunction do not have high dropout rates. By contrast, patients with liver dysfunction tend to undergo a much more dynamic decrease in organ function. In reviewing a number of recent phase I studies of antitumor agents, it has become apparent that a very high percentage of patients with severe hepatic disease are removed from study before completing one cycle of therapy.

H&O What other considerations does liver dysfunction raise in terms of clinical trials?

ME One of the issues raised by the rapid decline of patients with liver dysfunction is whether it is ethical to treat these patients, knowing that up to three quarters will not proceed past one cycle of therapy, in order to generate data that can be applied to subsequent patients with tumors that might respond to a particular drug.

It may be that we need to alter our criteria for dose-limiting toxicity. Is a two-fold increase in bilirubin a

sufficient reason to discontinue therapy? Right now, this criterion seems reasonable since drug-related toxicity cannot be ruled out as a cause of such an increase. However, clinical studies are always conducted with some therapeutic intent. A phase I study could not be conducted ethically if it was known that no enrolled patients would respond. A human toxicology study cannot be conducted if there is no goal, however remote, of response. Thus, the need to understand the activity of a drug in patients with organ dysfunction is sometimes at odds with the overall goals of therapeutic research.

With every study conducted, lessons are learned that are then incorporated into subsequent studies. The process of studying dose reduction in patients with organ dysfunction is not simple or straightforward. The studies being done today are much more specific than those conducted 10 years ago, or even 2 years ago. However, the studies still are not perfect and further advancements in our understanding are needed.

Suggested Reading

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