Dihydropyrimidine Dehydrogenase: Its Role in 5-Fluorouracil Clinical Toxicity and Tumor Resistance

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Dihydropyrimidine dehydrogenase (DPD) is the initial enzyme and the rate-limiting step in the pyrimidine catabolic pathway (1). Studies over the past two decades have demonstrated that DPD is an important regulatory enzyme in the metabolism of both the naturally occurring pyrimidines uracil and thymine as well as the cancer chemotherapy fluoropyrimidine drug, 5-FU (2). In particular, pharmacokinetic studies have demonstrated that 85% of clinically administered 5-FU is inactivated and eliminated through the catabolic pathway (3). However, the cytotoxicity of 5-FU in host and tumor cells only occurs following anabolism to nucleotides with the amount of 5-FU available for anabolism determined by the extent of its catabolism (4). Thus, a balance exists between the enzymatic activation of 5-FU and its catabolic elimination with the DPD enzyme being recognized as an essential factor in the overall regulation of 5-FU metabolism (2, 4).

Over the past several years, a number of clinical pharmacological studies with fluoropyrimidine drugs have highlighted the importance of DPD to 5-FU clinical pharmacokinetics, clinical toxicity, and tumor resistance (2). DPD is now known to be responsible for much of the observed variability in clinical pharmacokinetics of 5-FU. This includes both the variability in clinical pharmacokinetics of 5-FU within an individual patient as well as the variability observed within a population of patients. Within the same patient receiving 5-FU by continuous infusion, 5-FU levels have been observed to vary throughout the 24-h period with a circadian pattern. Accompanying this pattern is an “inverse” circadian pattern of DPD activity that is thought to be responsible for the varying 5-FU levels (5). The variable pharmacokinetics observed with 5-FU bolus infusions from patient to patient is now known to be due to the patient to patient variability in DPD activity that may differ as much as 6-fold in the general population (6). It has long been recognized that the bioavailability of 5-FU varies significantly between individuals (2, 7). Preclinical and clinical studies using DPD inhibitors have now shown that 5-FU is well absorbed with excellent bioavailability, following inhibition of DPD activity (particularly in the gastrointestinal tract; Refs. 2 and 8). Theoretically, knowledge of an individual’s DPD activity should allow for more appropriate dosing of 5-FU, avoiding the pharmacokinetic variability that in turn permits the maximal dose of 5-FU for antitumor effect while minimizing systemic toxicity. A somewhat different approach has been to maximally inhibit DPD activity using very potent DPD inhibitors to enable more predictable pharmacokinetic control and therefore more effective dosing of 5-FU (9).

There are several situations in which DPD activity is so decreased that severe and at times life-threatening 5-FU toxicity occurs. DPD deficiency is a pharmacogenetic syndrome in which molecular defects in the DPD gene result in a complete (profound) or partial loss of DPD enzyme activity (10, 11). This results in markedly altered 5-FU pharmacokinetics and in turn severe toxicity following administration of standard doses of 5-FU. The cause for this toxicity appears to be decreased drug clearance, resulting in markedly prolonged exposure to 5-FU (12). Although infrequent, this condition is not rare, with >20 cases having been described in the literature (with perhaps 30 additional cases to our knowledge having been detected but not published; Refs. 10 and 11). Drug interactions can also produce a similar life-threatening consequence. Perhaps the best example thus far has been the interaction between the anti-herpes zoster drug Sorivudine (5-bromovinyl-ara uracil) and standard doses of 5-FU, which resulted in 18 deaths. Studies have since shown that a metabolite of Sorivudine is a potent inhibitor of the DPD enzyme (13). The occurrence of DPD deficiency (profound or partial) in the population and the critical role of DPD in 5-FU pharmacokinetics have provided motivation for developing rapid, user-friendly assays for monitoring DPD activity prior to administration of 5-FU (14). Unfortunately, most of the methods available at present are not well suited for general clinical use.

More recently, several studies have demonstrated that DPD activity is not only important in determining 5-FU pharmacokinetics and clinical toxicity but also is a critical factor in determining the availability of 5-FU for anabolism to active metabolites within the tumor (15, 16). This raises the possibility that measuring the level of DPD activity within the tumor itself may have predictive value in determining whether the tumor is likely to respond to 5-FU. The use of biochemical assays, although valuable, is often not practical, particularly with the unavailability of sufficient clinical samples (e.g., needle biopsies). An alternative approach was described recently using molecular methodology (i.e., quantitation of DPD mRNA by reverse transcription-PCR) as a means of determining intratumor DPD levels (17). In the report by Uetake et al. in this issue of the journal (18), strong evidence is presented that DPD mRNA levels correlate with DPD enzyme activity. These data suggest an alternative method for determining DPD levels in samples where there is insufficient tissue to perform a DPD

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²The abbreviations used are: DPD, dihydropyrimidine dehydrogenase; 5-FU, 5-fluorouracil.
enzyme assay. Although there are still some limitations with the semiquantitative reverse transcription-PCR assay (17, 18), this report certainly provides further stimulus for examining the potential utility of this assay as a predictive pharmacogenomic assay in future clinical studies.

References
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