Clinical Implications of Dihydropyrimidine Dehydrogenase Inhibition

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Dihydropyrimidine dehydrogenase (DPD) is the initial, rate-limiting enzyme in the catabolism of 5-fluorouracil (5-FU). DPD has an important role in regulating the availability of 5-FU for anabolism. It is now clear that DPD also

Introduction

Dihydropyrimidine dehydrogenase (DPD), also referred to as dihydrouracil dehydrogenase, dihydrothymine dehydrogenase, uracil reductase, and EC 1.3.1.2), is the initial, rate-limiting enzymatic step in the catabolism of the naturally occurring pyrimidines, uracil and thymine, and the widely used antimetabolite cancer chemotherapy agent, 5-fluorouracil (5-FU).[1,2] As shown in Figure 1, DPD occupies an important position in the overall metabolism of 5-FU, converting more than 85% of administered 5-FU to the inactive metabolite 5-fluoro-5,6-dihydrouracil (5-FUH2) in an enzymatic step that is essentially irreversible.[3] Whereas anabolism is clearly critical in the conversion of 5-FU to the active nucleotides, 5-fluoro-2´-deoxyuridine 5´-monophosphate (FdUMP), 5-fluorouridine 5´-triphosphate (FUTP), and 5-fluoro-2´-deoxy-uridine 5´-triphosphate (FdUTP), catabolism controls the availability of 5-FU for anabolism, and thus occupies a critical position in the overall metabolism of 5-FU. FdUMP, FUTP, and FdUTP are, in turn, responsible for inhibition of cell replication through inhibition of thymidylate synthase or through incorporation into ribonucleic acid (RNA) or deoxyribonucleic acid (DNA), respectively.

Clinical Consequences of Modulation of DPD Activity

The importance of DPD to the clinical pharmacology of 5-FU has been further established by several recent observations (Table 1) that demonstrate that DPD can account for much of the variability that has been noted in clinical studies with 5-FU. This includes both intrapatient differences (circadian variation of drug levels) and interpatient variability (in pharmacokinetics, bioavailability, toxicity, and antitumor effectiveness) of 5-FU's clinical pharmacology.

DPD has been shown to follow a circadian pattern in both animals and humans.[4-6] This is thought to explain the variable plasma levels of 5-FU observed in patients receiving continuous 5-FU infusion by automated pumps. Studies have, in fact, demonstrated a circadian variation of tissue DPD levels associated with an inverse circadian pattern in plasma 5-FU concentrations. This has led some chemotherapists to propose time-modified 5-FU infusions to optimize drug delivery during a 24-hour period. In Western Europe, some oncologists have reported potential benefit with such regimens in the treatment of certain cancers.[7]

DPD enzyme activity in normal tissues (peripheral blood mononuclear cells and liver) has also been shown to vary from individual to individual in a normal distribution pattern, with as much as a sixfold variation from the lowest to the highest values.[8,9] This wide variation in DPD activity is thought to be responsible for the wide variation in the drug's half-life observed in patients in population studies.[10] In addition, it is now clear that a small percentage (< 5%) of the population has, without apparent reason, DPD activity significantly below the normal distribution that characterizes most of the population.[11-13] These individuals are at significant risk if they develop cancer and are administered 5-FU. This is a true pharmacogenetic syndrome, the symptoms of which are not recognized until the patient is exposed to the drug.[14]

Variation in DPD activity has also been shown to be responsible for the apparent variable bioavailability of 5-FU, which has historically led to recommendations against oral 5-FU administration. This understanding potentially explains the erratic bioavailability of a small molecule
with a $pK_a$ that should favor excellent absorption and bioavailability. Experimental studies of DPD inhibitors in animals reveal that inhibition of DPD following oral 5-FU administration yields a pharmacokinetic pattern essentially the same as that produced by intravenous administration, thus implying almost 100% bioavailability.[15] Tumors may also express variable DPD activity.[16] This may explain the inconsistent tumor response to 5-FU. A recent study of interest demonstrated increased DPD expression in tumors from patients who were resistant to 5-FU, even when thymidylate synthase expression was low.[17]

**Inhibition of DPD for Pharmacologic Gain**

The above studies relating inconsistent DPD activity to the observed variability in 5-FU pharmacology make it attractive to consider inhibiting DPD to eliminate the unpredictable variations. Inhibiting DPD in 5-FU susceptible host tissue, such as gastrointestinal (GI) mucosa and bone marrow, should make dosing from patient to patient less variable, avoiding the typical (with 5-FU and many other cancer chemotherapeutic agents) dosing decisions based on observed toxicity. Inhibition of DPD in tumor specimens is also attractive in that most tumors probably become resistant through increased intratumor DPD activity, leading to increased degradation and thus less anabolism of 5-FU. Over the years, there have been numerous attempts to synthesize effective inhibitors of DPD,[18] many of which turned out to be very toxic. In the past several years, new fluoropyrimidine drugs using DPD inhibition agents referred to as dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines (DIF) have been introduced to the clinic.

**DPD-Inhibitory Fluoropyrimidines**

There are currently four new DIF drugs (Table 2): UFT, ethynyluracil, S-1, and BOF-A2. These drugs differ both in type of DPD inhibition and the degree of inhibition produced. The rationale for using DIF drugs is shown in Table 3. Basically, 5-FU, derived either from 5-FU itself or from a prodrug converted to 5-FU, is administered together with another drug that interferes with (or inhibits) the otherwise rapid catabolism of 5-FU. All four of these drugs derive a therapeutic advantage from DPD inhibition. Most impressive are 1) the capacity for oral delivery of 5-FU (bioavailability > 70%), and 2) the leveling of 5-FU pharmacokinetic variability. In addition, inhibition of the catabolic pathway allows more 5-FU to enter the anabolic pathway, potentially increasing the antitumor effect. This may be particularly important for resistant tumors with increased DPD expression. Finally, at least some 5-FU toxicities (hand-foot syndrome, some forms of neurotoxicity, and possibly cardiotoxicity) may be secondary to the catabolic pathway, although this mechanism is not completely understood. Inhibiting the catabolic pathway should decrease the incidence of these toxicities.

**The DIF Drugs**

**UFT**

UFT was the first of the DIF drugs to be synthesized and is therefore the one with which we have the most experience.[19] This new fluoropyrimidine is a combination of the naturally occurring pyrimidine, uracil, and the 5-FU prodrug, tegafur, in a 4:1 molar ratio. The presence of uracil in excess of 5-FU results in competition at the level of DPD, such that 5-FU will not be rapidly degraded and will remain present for a prolonged period. Although this is not true inhibition of DPD, the competition between 5-FU and uracil for DPD produces an effect similar to what one achieves with a true DPD inhibitor. In contrast to the effects of true DPD inhibitors and inactivators, the effect of UFT on DPD is more rapidly reversible, thereby possibly avoiding some of the problems observed with the earlier DPD inhibitors. This alteration may account for a more favorable toxicity profile compared with the earlier DPD inhibitors,[18] as well as with some of the newer DIF drugs. Extensive data from Japan, as well as Europe, South America, and the United States, are now demonstrating that orally administered UFT has antitumor activity in several tumor types (particularly breast and colon cancer), either as a single agent or combined with calcium folinate.[20-22] It appears to be at least as effective as intravenous infusion of 5-FU. Furthermore, the toxicity profile is quite tolerable, with the typical fluoropyrimidine toxicities (eg, diarrhea and nausea) seen at the maximum tolerated dose. Of note is the near absence of other 5-FU toxicities, in particular hand-foot syndrome, neurologic effects, and cardiotoxicity.[23] Although not proven, these toxicities, which are thought to be secondary to 5-FU catabolites, may be eliminated by using a DIF drug such as UFT. Several articles within this supplement provide evidence of the efficacy and tolerable toxicity of UFT.
Ethynyluracil
Recently, a new DPD inhibitor, ethynyluracil (Eniluracil, or GW776C85), has been synthesized and demonstrated to be a potent inactivator of DPD.[15] This pyrimidine is structurally similar to both uracil and 5-FU.[24] In initial phase I clinical studies, ethynyluracil administration led to rapid and complete DPD inactivation, which was maintained for more than 1 day at clinical doses.[25,26] At present, a number of phase II studies are underway to evaluate the effectiveness of the coadministration of low-dose 5-FU and ethynyluracil in a number of different malignancies, including colorectal and breast cancer.

S-1
In Japan, there have been several attempts to further develop this concept. S-1 is a triple-drug combination consisting of the prodrug, tegafur, together with a DPD inhibitor, chloro-2,4-dihydroxyxypyridine (CDHP), plus potassium oxalate in a molar ratio of 1:0.4:1, respectively.[27] This combination not only provides sustained release of 5-FU via use of the prodrug and DPD inhibitor, but also utilizes potassium oxalate theoretically to lessen bothersome GI toxicity (particularly diarrhea). In preclinical studies, potassium oxalate has been shown to selectively inhibit 5-FU phosphorylation by the enzyme, orotate phosphoribosyltransferase, particularly in the GI tract, but not in a tumor.[28] Preclinical study results have demonstrated excellent antitumor activity.[29] Clinical studies thus far have shown S-1 to be quite tolerable.[30,31] United States studies of this drug have been limited.

BOF-A2
BOF-A2 represents another attempt to develop an improved fluoropyrimidine. With this two-drug combination, the prodrug 1-ethoxymethyl 5-fluorouracil (EM-FU) is combined with the DPD inhibitor 3-cyano-2,6-dehydropyrimidine (CNDP) in a 1:1 molar ratio.[32,33] EM-FU is relatively resistant to degradation and is metabolized to 5-FU by liver microsomes. Preclinical studies have confirmed antitumor activity in several animal models and have demonstrated sustained 5-FU levels resulting from the release of 5-FU by EM-FU. Clinical studies have been undertaken in Japan and, more recently, limited studies have been initiated in the United States. It is too early to comment on the clinical effectiveness of this drug combination. Thus far, BOF-A2 has demonstrated typical 5-FU toxicities, with some patients experiencing more severe toxicity such as mucositis and diarrhea. At present, the dose, schedule, and possible combination with other modulators (eg, calcium folinate) are being evaluated.

Conclusion
It is now clear that DPD is a critical step in pyrimidine metabolism and is responsible for much of the variability in pharmacokinetics, bioavailability, toxicity, and efficacy following administration of 5-FU. Inhibition of DPD activity through the use of DPD inhibitors should result in less variation in 5-FU pharmacokinetics and bioavailability. At the same time, inhibition of the DPD pathway should potentially improve the therapeutic effectiveness of 5-FU, both by making toxicity more predictable and by overcoming the high levels of DPD activity that may be a source of resistance in tumors. The recent availability of DIF drugs provides a means by which 5-FU may be administered orally at reduced doses, producing an effect similar to continuous infusion of 5-FU without significant intrapatient or interpatient variability in 5-FU pharmacokinetics. Clinical studies thus far demonstrate tolerable toxicities. Clinical trials are currently underway to evaluate the therapeutic effectiveness of each of these drugs.

References:


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