GW776C85 is a new drug that has been shown to be an effective inactivator of dihydropyrimidine dehydrogenase (DPD). Preclinical studies demonstrated that administration of GW776C85 with 5-fluorouracil (5-FU) resulted in several desirable pharmacologic effects. Initial clinical data on 5-FU combined with GW776C85 suggest potentially increased antitumor activity in at least some malignancies with tolerable toxicity, as well as several distinct economic and quality-of-life advantages including the following: (1) The possibility of administering 5-FU as an oral drug due to excellent bioavailability of 5-FU following inactivation of DPD; (2) a cost-effective alternative to continuous or protracted infusion of 5-FU without the need for hospitalization or surgical placement of an intravenous access and availability of an ambulatory pump; and (3) potential for less interpatient variation of 5-FU toxicity (eg, in host tissues, such as bone marrow and gastrointestinal mucosa cells) due to inactivation of DPD in essentially all patients treated, permitting better 5-FU dosing guidelines. Finally, because tumors may theoretically become resistant to 5-FU by increased levels of DPD, the use of GW776C85 to inactivate DPD may provide a potential means by which tumor resistance can be reversed. [ONCOLOGY(Suppl 4):51-56, 1998]

Dihydropyrimidine dehydrogenase (dihydouracil dehydrogenase, dihydrothymine dehydrogenase, uracil reductase, EC 1.3.1.2, DPD) is the initial rate-limiting enzymatic step in the catabolism of not only the naturally occurring pyrimidines uracil and thymine, but also the widely used antimetabolite cancer chemotherapy agent 5-fluorouracil (5-FU).[1,2] DPD thus occupies an important position in the overall metabolism of 5-FU, converting over 85% of clinically administered 5-FU to 5-FUH₂, an inactive metabolite, in an enzymatic step that is essentially irreversible (Figure 1).[3] While anabolism is clearly critical in the conversion of 5-FU to the "active" nucleotides FdUMP, FUTP, and FdUTP (which, in turn, can inhibit cell replication through inhibition of thymidylate synthase, or through incorporation into RNA or DNA, respectively), catabolism controls the amount of 5-FU available for anabolism and thus occupies a critical position in the overall metabolism of 5-FU.

Methods to Assess DPD Activity

It is thus desirable to be able to assess DPD activity, particularly when evaluating fluoropyrimidine catabolism in the clinical setting. We currently use three different methods to measure DPD activity. Two of the methods are direct assays of DPD activity; one is an HPLC-radioassay for DPD activity and the other is an immunoblot assay of DPD protein.[3] A third method useful mainly in the in vivo or clinical setting is an indirect assessment of DPD activity. By quantitating the levels of uracil, the natural substrate for DPD that increases when DPD is inhibited, the remaining DPD activity can be estimated.[4]

For most clinical studies of DPD activity, peripheral blood mononuclear cells, isolated from heparinized blood on Ficoll-hypaque, can be used to monitor for DPD activity. Two of the methods are direct assays of DPD activity; one is an HPLC-radioassay for DPD activity and the other is an immunoblot assay of DPD protein.[3] A third method useful mainly in the in vivo or clinical setting is an indirect assessment of DPD activity. By quantitating the levels of uracil, the natural substrate for DPD that increases when DPD is inhibited, the remaining DPD activity can be estimated.[4]

Important of DPD for 5-FU Pharmacology

The importance of DPD to the clinical pharmacology of 5-FU has been further emphasized by results of several recent studies (Figure 3) that demonstrate how DPD can influence the pharmacokinetics, bioavailability, toxicity, and antitumor effectiveness of 5-FU.
DPD is now known to follow a circadian pattern in both animals and humans.[6-8] Studies in patients receiving 5-FU infusion by automated pumps have demonstrated that the circadian variation of tissue DPD level is accompanied by an inverse circadian pattern in plasma 5-FU concentrations. This has potential importance in the design of time-modified 5-FU infusions. Such regimens have been suggested to have potential benefit in the treatment of certain human cancers.[9] DPD enzyme activity in normal tissues (peripheral blood mononuclear cells and liver) has also been shown to vary from person to person in a gaussian pattern, with as much as a 6-fold variation from the lowest to the highest values.[10,11] This wide variation in DPD activity is likely responsible for the wide variation in the t½ observed in patients in population studies.[12] In addition to the variation of DPD activity in the normal population, it is clear now that an additional small percentage (< 7%) of the population has DPD activity significantly below the gaussian distribution that characterizes most of the population.[13-15] These individuals are at significant risk if they develop cancer and are given 5-FU. Thus, this is a true pharmacogenetic syndrome with symptoms that are not recognized until patients are exposed to the drug.[16] The variation in DPD activity has also been shown to be responsible for the apparent variable bioavailability of 5-FU. Reasons for the erratic bioavailability of 5-FU have not previously been clear, particularly because it is a small molecule with a pKa that should result in excellent absorption and bioavailability. Experimental studies in animals given DPD inhibitors have demonstrated that, following inhibition of DPD, the pharmacokinetic pattern resulting from oral administration of 5-FU is essentially the same as that produced by IV administration, suggesting almost 100% bioavailability.[17] Tumors may also express a variable level of DPD activity.[18] This potentially may explain the observed varied tumor response to 5-FU. Thus, tumors with high DPD levels are relatively resistant to 5-FU, while tumors with low levels of DPD are relatively sensitive.

**Pharmacologic Modulation of DPD**

The studies described above detailing the variability in DPD levels in both normal and tumor tissues provide an explanation for the observed variability in 5-FU pharmacology. It thus becomes attractive to consider inhibiting DPD in order to eradicate the variability in 5-FU pharmacology. Inhibiting DPD in 5-FU-susceptible host tissue, such as GI mucosa and bone marrow, should make dosing from patient to patient less variable with this typical cancer chemotherapeutic agent in which dosing decisions are typically based on observed toxicity. Inhibition of DPD in the tumor is also attractive because it is likely that many tumors achieve resistance to 5-FU through an increase in DPD activity within the tumor, resulting in increased degradation and thus less anabolism of 5-FU. Over the years, there have been many attempts to synthesize effective inhibitors of DPD.[19] Unfortunately, many of these compounds have proven to be very toxic. Recently, a new DPD inhibitor, ethynyluracil or GW776C85, has been synthesized and demonstrated to be a potent inactivator of DPD.[20] This compound is a pyrimidine (Figure 4) with a structure similar to that of both uracil and 5-FU.

**Preclinical Studies With GW776C85**

Preclinical studies using GW776C85 to produce inactivation of DPD as a novel pharmacologic approach have been encouraging, with results demonstrating improved effectiveness of 5-FU. In murine studies, GW776C85 at relatively low doses rapidly and completely inactivated DPD and produced no obvious toxicity in animals exposed over prolonged periods in chronic toxicity studies of GW776C85 alone.[21] A concomitant increase in plasma uracil levels was observed in these animals following inhibition of DPD.[22] Identification of an effective, non-toxic dose of GW776C85 has, in turn, permitted evaluation of this drug together with various low doses of 5-FU. Initial pharmacokinetic studies demonstrated reproducible 5-FU pharmacokinetics in rodents.[23] Subsequent rodent studies showed that 5-FU could be administered orally reproducibly in intra-animal and inter-animal studies; bioavailability was demonstrated to be approximately 100%.[17] The effectiveness of 5-FU and GW776C85 in inhibiting tumor growth has now been demonstrated in several animal models, with evidence of complete tumor regression in some of these models in which only modest antitumor effect had previously been seen.[21]

**Initial Clinical Studies With GW776C85**
Initial phase I clinical studies with GW776C85 examined administration of the drug alone orally for 7 days at doses of 0.74, 3.7, or 18.5 mg/m² to determine both the initial clinical pharmacologic characteristics and the toxicity profile. Pharmacokinetic evaluation demonstrated a $t_{1/2}$ of 4.5 h for each of these doses. No changes in the pharmacokinetics of GW776C85 were observed with repeated doses compared with single doses.[24]

Of particular interest is the effect of these doses of GW776C85 on DPD activity in the clinical setting. To assess DPD activity, we used peripheral blood mononuclear (PBM) cells, as described above. DPD activity was measured as outlined in Figure 2. These studies demonstrated that DPD was rapidly and completely inactivated by GW776C85, and inhibition was maintained for more than 1 day at clinically used doses.[25]

**Planned Clinical Trials With GW776C85**

At present, several phase II studies are under way or being planned to evaluate the effectiveness of coadministration of 5-FU and GW776C85 to patients with different malignancies, most of which are gastrointestinal tumors. Current or planned studies include institutional as well as cooperative group trials in the US, Europe, and Asia. These trials aim to confirm whether administration of GW776C85 results in more predictable and rational dosing with 5-FU, and whether chemotherapy effectiveness improves as a result of eliminating 5-FU degradation by tumor DPD. The trials will also evaluate ease of use, because the GW776C85 and 5-FU regimen should allow oral administration of 5-FU and avoids the inconvenience and expense of chronic intravenous access and an ambulatory pump. Finally, these trials, particularly phase III trials, will assess whether the occurrence of bothersome 5-FU toxicities, such as hand-foot syndrome, cardiotoxicity, and neurotoxicity, are lessened in patients receiving a DPD inhibitor compared with those who receive 5-FU continuous infusion. Although the precise mechanisms of these toxicities are not known, they are thought to be related to 5-FU catabolism.

**Economic and Quality-of-Life Factors**

It should be emphasized that in addition to the potential pharmacologic benefits and improved antitumor efficacy, use of GW776C85 may result in several economic and quality-of-life benefits. Most important is that 5-FU can now be administered by the oral route, resulting in potential cost savings and ease of drug administration. Orally administered GW776C85 together with 5-FU provides an alternative to protracted infusion of 5-FU, obviating the need for surgical placement of a venous access, rental of an ambulatory infusion pump, and the cost of intravenous infusion supplies. This regimen also provides a cost savings compared with 5-FU bolus regimens, which require frequent office visits or 4- or 5-day continuous infusions that typically require hospitalization. Finally, assuming that a patient receives a minimum of equal antitumor effectiveness without increased toxicity compared with traditional 5-FU regimens, oral administration of 5-FU with GW776C85 offers a more appealing therapy.

**Conclusions**

DPD is a critical step in pyrimidine metabolism and is responsible for much of the variability in the pharmacokinetics, bioavailability, toxicity, and efficacy of 5-FU. Inhibition of DPD activity through inactivation of the enzyme should result in less variation in 5-FU pharmacokinetics and bioavailability and potentially may improve the drug's therapeutic effectiveness, both by making toxicity with 5-FU dosing more predictable and by overcoming the high levels of DPD activity in the tumors. The recent availability of the DPD inactivator GW776C85 provides a means by which 5-FU may be administered orally at reduced doses, producing an effect similar to that achieved with continuous infusion of 5-FU, without significant interpatient or intrapatient variability in 5-FU pharmacokinetic characteristics. Preliminary clinical studies demonstrate tolerable toxicities. Clinical trials are under way to evaluate the therapeutic effectiveness of the combined administration of 5-FU and GW776C85 in several tumor types.

**Discussion**

**Dr. Weeks:** Clinicians are soon going to be faced with several oral 5-FU strategies. Are there reasons to think these strategies would provide variable results or do they need to be tested head to head? How will physicians make sense of studies comparing oral 5-FU with intravenous
administration?

**Dr. Diasio:** That is a good question, the answer to which we do not have at this point. Several different agents that inhibit DPD are becoming available for use with 5-fluorouracil clinically in the United States, Europe, and Japan, but as of yet there have not been any head-to-head comparisons. The point I would emphasize with GW776C85 is predictability. This agent offers a method to control the administration of 5-FU. In my laboratory, we have assessed several other DPD inhibitors and have found that not all of the inhibitors offer the predictability that results from GW776C85 administration, most likely because the latter is a complete inactivator of DPD. Another point I would emphasize, which has now been demonstrated in several studies, is that increased levels of DPD in tumors provide a mechanism of resistance by which tumors can escape the effects of 5-FU. Thus, it is desirable to control tumor DPD levels. GW776C85 should make this possible.

**Dr. Hillner:** In subsequent studies of GW776C85, should the control arm be adjusted for the circadian variation of DPD activity?

**Dr. Diasio:** No. Although our previous studies have emphasized the importance of the circadian pattern of DPD, as well as the importance of the pharmacogenetics of DPD deficiency, it should be emphasized that the effects of both DPD deficiency and the circadian variation of DPD activity are basically removed by the presence of a DPD inhibitor. That is an additional positive feature of using such an agent.

**References:**


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