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## Dihydropyrimidine Dehydrogenase and Treatment by Fluoropyrimidines

*Past and Future Directions*

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### 1. INTRODUCTION

5-Fluorouracil (5-FU) is still one of the most commonly prescribed anticancer drugs, with activity against cancers of the gastrointestinal tract, head and neck, and breast. In addition, new oral 5-FU prodrugs like UFT, S<sub>1</sub>, capecitabine are emerging in the arena of the new drugs in oncology (1,2). Thus, treatment by fluoropyrimidines including 5-FU itself or its prodrugs represents a significant part of the chemotherapy agents currently in use or under investigation. The administration of oral fluoropyrimidines underscores the importance of the enzyme dihydropyrimidine dehydrogenase (DPD), which not only controls the catabolic route of 5-FU but also limits its oral absorption (3). In addition, DPD inhibition represents a major objective for the development of oral fluoropyrimidines like UFT and S<sub>1</sub> (4). DPD has highest activity in liver and mononuclear cells, but is also found in most human tissues. The aim of this chapter is to cover the role of DPD in treatment by fluoropyrimidines with considerations on the link between DPD and 5-FU pharmacokinetics, the importance of DPD deficiencies, the existence of DPD circadian rhythm with its clinical consequences, the comparison between DPD genotyping and DPD phenotyping, the role of DPD in 5-FU resistance in vitro and in vivo, and the role of DPD inhibition in the development of new oral fluoropyrimidines.

## 2. DPD AND PHARMACOKINETICS OF 5-FU

More than 80% of an administered dose of 5-FU is eliminated by catabolism through DPD, the rate-limiting enzyme (3). DPD activity is found in most tissues, exhibiting the highest activity in the liver (5). However, peripheral blood mononuclear cells (PBMC) are used for clinical monitoring of DPD activity, as these cells are obviously more accessible than hepatic tissue. We reported on a significant, but weak ( $r^2 = 0.32$ ), correlation between PBMC and liver DPD activity (6). This observation validates the use of DPD determination in PBMC for estimating the individual capacity to clear 5-FU. It is however important to mention that marked discrepancies may exist between hepatic and PBMC-DPD activity particularly in the case of patients with altered liver function who can exhibit a low DPD activity and a normal PBMC-DPD activity (7). The evidence of an association between DPD activity in PBMC and plasma 5-FU concentration was initially published a decade ago by the group of R. Diaso (8). The relationship between PBMC-DPD activity and 5-FU systemic clearance was then evaluated by Fleming and associates (9). A significant linear correlation was observed between PBMC-DPD activity and 5-FU clearance (9,10). However, this relationship is very weak ( $r^2 = 0.10$ ), and we feel that simply determining PBMC-DPD is not sufficient to accurately predict 5-FU clearance. The NONMEN population pharmacokinetic analysis that we conducted had the aim to identify patient covariables, which could influence interpatient variability in 5-FU clearance (10). 5-FU clearance was significantly reduced by increased age, high serum alkaline phosphatase, length of infusion, and low PBMC-DPD. However, a relatively high error was found in the estimate between observed and predicted 5-FU clearance and thus this multifactorial approach including PBMC-DPD did not allow faithful 5-FU dose adaptation prior to treatment. In addition, DPD activity may vary from one cycle to the other without any evidence of a trend for an increase or decrease during the treatment course (9). McLeod and coworkers conducted a clinical study and an experimental study on laboratory animals, aiming to examine the evolution of DPD activity under 5-FU treatment (11). They found that PBMC-DPD decreased by a median of 39% following the administration of 5-FU ( $p = 0.001$ ). In addition, 5-FU induced alterations in rat liver DPD were noted by these authors with the lowest activity occurring 48 h after drug administration (11). In total, PBMC-DPD-based 5-FU dose adaptation strategy is not justified in our opinion. However, marked 5-FU dose reductions can be proposed for patients showing more or less marked DPD deficiency (*see below*).

## 3. DPD DEFICIENCIES

Lu and associates (12) were the first to provide population data on DPD activity and demonstrated a Gaussian distribution for PBMC-DPD in 124 healthy subjects. Prospective studies on 185 unselected cancer patients and 75 colorectal cancer patients were performed (13,14). In these populations, DPD activity also showed an unimodal distribution and no subject with complete DPD deficiency was identified in these studies. Multifactorial analysis of variance showed that neither liver function tests (biological evaluation) nor age influenced DPD activity. It was also found that DPD activity was, on average, 15% lower in women as compared with men ( $p = 0.03$ ) (14). Interestingly, this 15% difference in DPD activity is the same order as the difference observed in 5-FU clearance between men and women (15). However, in the study by Lu and colleagues, DPD activity was not influenced by sex (12). The discrepancy in the effect of gender on DPD activity between these studies could be explained by the difference in the age range covered, with influences from the hormonal status: Premenopausal women were the majority in the Lu study (12) vs postmenopausal

women in the majority studied by Etienne and colleagues (14). However, this hypothesis could not be confirmed from the limited set of women studied ( $n = 33$ ), since no difference in DPD activity was demonstrated between pre- and postmenopausal women. We recently reported PBMC-DPD data concerning a group of 53 patients (23 men, 30 women) (16) treated by 5-FU-based chemotherapy in different French institutions and who developed unanticipated 5-FU-related toxicity. Among the whole group of 53 patients, 19 had a significant DPD deficiency (DD; below 150 fmol/min/mg protein, i.e., less than 70% of the mean value observed from previous population study). There was a greater majority of women in the DD group (15 out of 19, 79%) compared with the remaining 34 patients (15 out of 34, 44%,  $p < 0.014$ ). Toxicity was often severe, leading to patient death in two cases (both women). The toxicity score (sum of WHO grading, theoretical range 0–20) was twice as high in patients with marked DD (below 100 pmol/min/mg protein,  $n = 11$ , mean score = 13.2) compared with patients with moderate DD (between 150 and 100 pmol/min/mg protein,  $n = 8$ , mean score = 6.8),  $p = 0.008$ . In the DD group, there was a high frequency of neurotoxic syndromes (7 out of 19, 37%). The two deceased patients both had severe neurotoxicity. The occurrence of cardiac toxicity was relatively rare (1 out of 19, 5%). These data confirm that women are particularly prone to DPD deficiency. In total, from these above-discussed studies, it is clear that complete DPD deficiency is a very rare event. However, if we consider the PBMC-DPD value of 100 pmol/min/mg protein as the upper threshold indicative of an increased risk for developing 5-FU-related toxicity (16), one can estimate that approx 3% of an unselected group of cancer patients are located below this threshold value (14). DPD-associated morbidity, and in some cases mortality, among patients who often do not have detectable disease (adjuvant therapy) has great personal and economic implications. It follows that, in our opinion, the practical interest to determine DPD before 5-FU treatment must be carefully weighed in terms of cost–benefit balance. Current methods, requiring PBMC isolation and high performance chromatography analysis, are difficult to apply for general screening. In addition, Van Kuilenburg and colleagues have recently reported on a positive correlation they observed between DPD activity in PBMC and the percentage of monocytes (17). The proportion of monocytes can vary during anticancer treatment, thus the variable proportion of monocytes in PBMC can introduce intra- and interpatient variability in DPD activity determination. An interesting alternative approach to identify DPD deficient patients could be to use surrogate markers like the dihydrouracil ( $\text{UH}_2$ )–uracil (U) ratio, easy to determine in plasma before treatment; Gamelin and coworkers recently reported on this ratio, which was determined in a group of 81 patients with advanced colorectal cancer receiving weekly infusions of 5-FU–folinic acid (18). They found that the  $\text{UH}_2$ –U ratio was normally distributed and was correlated to 5-FU clearance ( $r = 0.64$ ). Interestingly, toxic side effects were observed only in patients with initial  $\text{UH}_2$ –U ratio of less than 1.8.

#### 4. CIRCADIAN RHYTHM OF DPD

The existence of a circadian rhythm for DPD activity has been suggested from both human and animal investigations (19). Harris and associates (8) measured lymphocyte DPD activity and 5-FU plasma concentrations in cancer patients receiving 5-FU by protracted continuous infusion. A circadian rhythm was observed in 5-FU plasma concentrations with a peak observed at 11 AM and a trough at 11 PM on average. The inverse relationship observed between the circadian profile of 5-FU plasma concentration and PBMC-DP activity suggested a link between DPD activity and 5-FU pharmacokinetics. Our group performed a pharmacokinetic study of FU in patients treated by continuous venous infusion of a

constant rate for 5 d (20). All patients had stage C bladder carcinoma and received *cis*-diamminedichloroplatinum (II) (45–91) mg/m<sup>2</sup> on d 1 as 30-min venous infusion at 5 PM. Continuous venous infusion of 5-FU (450–966 mg/m<sup>2</sup>/day) was started on d 2 at 8:30 AM via a volumetric pump and lasted for 5 d (until d 6). Blood samples were obtained every 3 h on d 2, d 4, and d 6 on each patient (20 samples/patient). Data were analyzed by both multiple analysis of variance and cosinor. Mean lowest and highest 5-FU plasma concentrations ( $\pm$  SEM) were, respectively, 254  $\pm$  33 ng/mL at 1 PM and 584  $\pm$  160 ng/mL at 1 AM ( $p < 0.03$ ). Both analysis of variance and cosinor analysis further validated ( $p < 0.0001$ ) a circadian rhythm with a double amplitude (total extent of variation) of 50% of the 24-h mean and an acrophase located at approx 1 AM (estimated time of peak). It was thus felt that circadian modulation of the infusion rate of 5-FU may further optimize the therapeutic index of such treatment modality. Besides continuous venous infusion, the impact of the time of drug administration was also studied for short venous infusions by Nowakowska-Dulawa (21). 5-FU (15 mg/kg) was administered in over 15 min every 4 d for 12 d and this at various times during the day. The authors noted marked differences in pharmacokinetic parameters and clearance value was found to be 70% at 13.00 h as compared to 01.00 h. Several studies have described a wide interindividual variation in peaks and troughs in DPD activity (22,23). More precisely, in the work recently reported Grem and coworkers (23) the authors wished to determine whether peak and trough in DPD activity occurred at uniform times in six subjects, whether individual patterns fit a discernible profile and whether such patterns were consistent and reproducible over time. In that purpose mononuclear cells were isolated from peripheral blood at 3-h intervals over a 24-h period on three different dates over a 6-mo period. When the data were averaged by study date for each subject, the median value for the average DPD activity was significantly different from both the median peak and median trough activities. Within the six subjects, the average DPD activity for the three study dates differed by a median of 2.4-fold. The time at which peak and trough DPD activities occurred varied between subjects: 8 of the 17 peaks (47%) occurred between 10:00 PM and 6:00 AM, 6 (35%) occurred between 8:00 AM and 3:00 PM, and 3 (18%) occurred between 5:00 PM and 8:15 PM. Thus, it could be concluded by the authors that the time of day when the peak occurred was essentially randomly distributed over the 24-h period of observation ( $p = 0.68$ ). Sixty percent of the trough DPD activities occurred between 7:00 AM and 3:00 PM. The median interval between the peak and trough was 6.5 h. When the combined data for all cycles was considered, the trough occurred 6–9 h after the peak, and the DPD levels subsequent to the peak did not display merely random variation ( $p = 0.0055$ ). The authors concluded that DPD activity levels and the times at which peak and trough DPD activities occurred varied both between and within subjects. A limitation from this latter study may be the fact that subjects were not synchronized.

## 5. DPD GENOTYPING VS DPD PHENOTYPING

Chromosome mapping of human *DPYD* gene was first described in 1994 (24). *DPYD* gene is located on chromosome 1 (1p22). *DPYD* gene is a large gene (> 950 kb) containing 23 exons leading to 3 kb of coding region (25,26). Seventeen *DPYD* mutations have been reported (27); these mutations lead to single amino acid substitutions, nucleotide deletions, or a donor splice site mutation resulting in exon skipping (GA mutation in the exon 14 splice site, 27). This latter mutation results in the production of a truncated mRNA and has been consistently associated with low DPD activity and 5-FU toxicity. In addition, Van Kuilenburg reported that this mutation was found in 8 out of 11 patients suffering from a complete

deficiency of DPD (28). More recently, Johnson and coworkers identified this latter molecular defect as being responsible for a complete lack of DPD enzymatic activity having induced a life-threatening toxicity in a patient treated by topical 5-FU (29). A molecular study was conducted in a cohort of cancer patients with reduced or normal DPD activity with the aim to analyze the 10 *DPYD* exons (exons 2, 4, 7, 10, 11, 13, 14, 18, 21, 23), where *DPYD* mutations were previously identified, (27). From this study a patient with a heterozygous intron 14G1A mutation had normal DPD activity. Kouwaki and colleagues undertook an expression analysis for three mutant *DPYD* genes found in Japanese patients (30). Only two mutations led to mutant DPD proteins with significant loss of enzymatic activity; the third one, however, resulted in no decrease in enzymatic activity compared with the wild-type. The conclusion from these studies is that *DPYD* mutations do not entirely explain polymorphic DPD activity and toxic response to 5-FU.

## 6. DPD IN TUMORS AND RESISTANCE TO 5-FU-BASED THERAPY

DPD activity can be considered as a potential factor for controlling 5-FU responsiveness at the tumoral level. The concept is simple: A high level of tumor DPD would metabolize 5-FU to inactive products before cytotoxic nucleotides can be formed. The potential role of DPD for influencing 5-FU activity also concerns new 5-FU prodrugs like UFT or capecitabine, where 5-FU is metabolically produced at the target site. Previous in vitro data revealed that DPD activity in tumor cells was significantly related to 5-FU sensitivity (31); the lower the DPD enzymatic activity, the greater the cytotoxicity. Interestingly, from this experimental study it was shown that DPD activity and thymidylate synthase activity were independent variables significantly correlated with 5-FU cytotoxic activity. Recent studies in human cancer xenografts demonstrated that the efficacy of capecitabine correlated very well with the ratio of thymidine phosphorylase/DPD (32). The role of tumoral DPD activity was then evaluated in the clinical setting. For head and neck cancer patients, DPD activity was detectable in all tumor samples (median tumoral DPD activity was 60, range 13–193 pmol/min/mg protein) (33). Tumoral DPD activity was not influenced by tumor staging. The patients with a complete response to 5-FU-based induction chemotherapy, exhibited lower tumoral DPD activities as compared with partial or nonresponding patients (33). In an attempt to reduce the variability due to confounding factors, including a possible circadian variability for DPD activity, we tested a normalized DPD value defined as the tumoral:adjacent nontumoral ratio of DPD activity. Interestingly, the distribution of normalized DPD revealed that complete responders exhibited a significantly lower normalized DPD than partial or nonresponding patients ( $p = 0.03$ ) (33). However, the tumor:normal tissue ratio is not the same for all tumor types. A recent study of 63 colorectal tumors found a median tumor:normal ratio of 0.76 (34). Although a subset of patients did have up to three times higher tumor DPD, the majority of patients had highest DPD in adjacent normal tissue. Although resistance to 5-FU is multifactorial, it can be considered that tumoral DPD activity may be a determining factor for 5-FU responsiveness in a subset of cancer patients. These data provide further pharmacological rationale for the use of DPD-specific inhibitors.

## 7. DPD INHIBITORS

There were recently four agents under development that interacted with DPD activity (Table 1); 5 ethynyluracil was the only one that is a DPD inactivator (irreversible inhibition)

**Table 1**  
**5-FU Oral Prodrugs Under Clinical Evaluation that Contain a DPD Inhibitor**

<i>Compound</i>	<i>Chemical name</i>	<i>Effect on DPD</i>
Eniluracil (Glaxo-Wellcome)	5-Ethynyluracil	Inactivator
UFT (Orzel <sup>(R)</sup> , Bristol-Myers Squibb, contains UFT plus leucovorin)	Uracil + tegafur	Inhibitor
S1 (Bristol-Myers Squibb)	5-Chloro-2, 4 dihydropyridine + tegafur + potassium oxonate	Inhibitor
BOF-A2 (Emitefur <sup>(R)</sup> , Otsuka America Pharmaceutical)	1-Ethoxymethyl-5-fluorouracil + 3-cyano- 2,6-dihydropyrimidine	Inhibitor

while the three others act as DPD inhibitors (competitive inhibition). Details on the clinical development on these compounds will be given in other chapters in this book. We will insist on the main characteristics of these DPD inhibitors. With 5-ethynyluracil pretreatment, the bioavailability of 5-FU becomes complete and thus renal clearance becomes the main source of drug elimination with significant correlations having been shown between 5-FU clearance and creatinine clearance (35). A consequence could be that dosage reductions would need to be made in patients with reduced renal function who are candidates for 5-ethynyluracil and 5-FU combined treatment. Competitive inhibitors of DPD activity are also part of the new products UFT, S<sub>1</sub>, and BOF-A<sub>2</sub>. UFT contains uracil and tegafur in a 4:1 ratio and S<sub>1</sub> includes 5-chloro-2,4-dihydropyrimidine (CDHP) in combination with tegafur and potassium oxonate. BOF-A<sub>2</sub> is an oral prodrug of 5-FU and 3-cyano-2,6-dihydropyrimidine (CNDP). CNDP is a much stronger DPD inhibitor compared to uracil. When uracil, CDHP or CNDP compete with 5-FU for the uracil binding site on the DPD protein, more 5-FU can be activated through the anabolic pathway. The consequence of competitive inhibition is that the effects of this inhibition are rapidly reversible; in comparison, a single dose of 5-ethynyluracil maintains a complete DPD inhibition for several days (36). A striking feature of the DPD inhibitor clinical studies is the very low incidence of hand/foot syndrome. In comparison, capecitabine, another 5-FU oral prodrug that does not contain a DPD inhibitor, induces a relatively high frequency of more or less severe hand/foot toxicity (37). It is thought that the presence of 5-FU related hand/foot syndrome can be due to the production of 5-FU catabolites that are absent when a DPD inhibitor is associated to the 5-FU oral prodrug. One of the major critical points for the clinical use of DPD inhibitors is to define the dose of DPD inhibitor so as to permit a significant inhibition of DPD activity to take place in the organism but to also keep a basal level of DPD activity in normal cells (intestinal, hematological) to maintain a minimal level of 5-FU detoxification through DPD activity.

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