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REVIEW ARTICLE

Tetsuro Kubota

5-Fluorouracil and dihydropyrimidine dehydrogenase

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Abstract Dihydropyrimidine dehydrogenase (DPD) is a rate-limiting enzyme of (fluorinated) pyrimidine degradation that plays a significant role in the pharmacokinetics of 5-fluorouracil (5-FU). In addition, a catabolite of 5-FU induces a certain toxicity, and the sensitivity of 5-FU is determined by DPD activity in tumors. DPD is thus important clinically. Drugs have been developed that control variations of the pharmacokinetics of 5-FU by controlling or inhibiting DPD, thereby reducing toxicity and improving sensitivity. These fluorinated pyrimidines with DPD-inhibiting activity, called DPD-inhibitory fluoropyrimidines, contribute to oral therapy with 5-FU for cancer. This paper summarizes the important role of DPD in cancer chemotherapy with 5-FU.

Key words 5-Fluorouracil · Dihydropyrimidine dehydrogenase (DPD) · DPD-inhibitory fluoropyrimidines (DIFs)

Introduction

5-Fluorouracil (5-FU), first synthesized by Heidelberger et al. in 1957,[1] has been employed for the treatment of various solid cancers for more than 45 years. In Japan, 5-FU derivatives such as tegafur, doxifluridine (5′-DFUR), and a mixed compound of tegafur and uracil at a molar ratio of 1:4 (UFT) have been developed since the 1970s and employed in oral therapy for cancer. In the United States and Europe, the development of UFT/leucovorin (LV), capecitabine, eniluracil/5-FU, 1 M tegatur – 0.4 M gimeracil – 1 M ostacil potassium (S-1), and so on began during the 1990s, and oral cancer therapy with fluorinated pyrimidines has attracted attention.[2,3]

Among these agents, UFT/LV, eniluracil/5-FU, and S-1 are classified as dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidines (DIFs)[4,5] (Table 1). Literally, they are fluorinated pyrimidines that have been developed for the purpose of inhibiting DPD (EC 1.3.1.2). This paper summarizes the importance of DPD in chemotherapy, mainly regarding 5-FU and its control.

T. Kubota (✉)
Department of Surgery, School of Medicine, Keio University,
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
Tel. +81-3-3353-1211, ext 62334; Fax +81-3-3355-4707
e-mail: tkubota@sc.itc.keio.ac.jp

Roles of DPD in the pharmacokinetics of 5-FU

Dihydropyrimidine dehydrogenase is an enzyme that catalyzes the first, rate-limiting step of (fluorinated) pyrimidine degradation[6] (Fig. 1). It is known to exhibit high activity in the liver and mononuclear cells, and its activity is widely distributed in a variety of organs, such as the small intestinal mucosa.[7,8] The liver is thought to limit the rate of degradation, however, because it has a relatively large volume. Aboagye et al.[9] reported that 96% of 5-FU exposed to the liver is degraded. In fact, the elimination half-time ($T_{1/2}$) of 5-FU administered in blood is only about 20 min.[6]

Although 5-FU is mainly degraded in the liver, it is not easy to collect samples for measuring DPD activity. Peripheral mononuclear cells (PMNCs) that exhibit a weak positive linear correlation with DPD activity in the liver are used as surrogate markers,[10] and DPD activity in PMNCs (PMNC-DPD) is inversely correlated with clearance of 5-FU.[11,12] PMNC-DPD activity is also known to exhibit circadian variations and to be involved in variations of blood 5-FU concentrations during intravenous infusion.[13] PMNC-DPD exhibits, however, large intra- and interindividual variation.[14] It is also reported that measurements of DPD activity vary depending on the composition of the PMNCs (proportions of lymphocytes and monocytes) and the protein level.[15]

Relation between DPD and 5-FU-related toxicity

Genetic DPD deficiency

Since the report by Tuchman et al. in 1985,[16] a relation between severe 5-FU toxicity and low DPD activity has

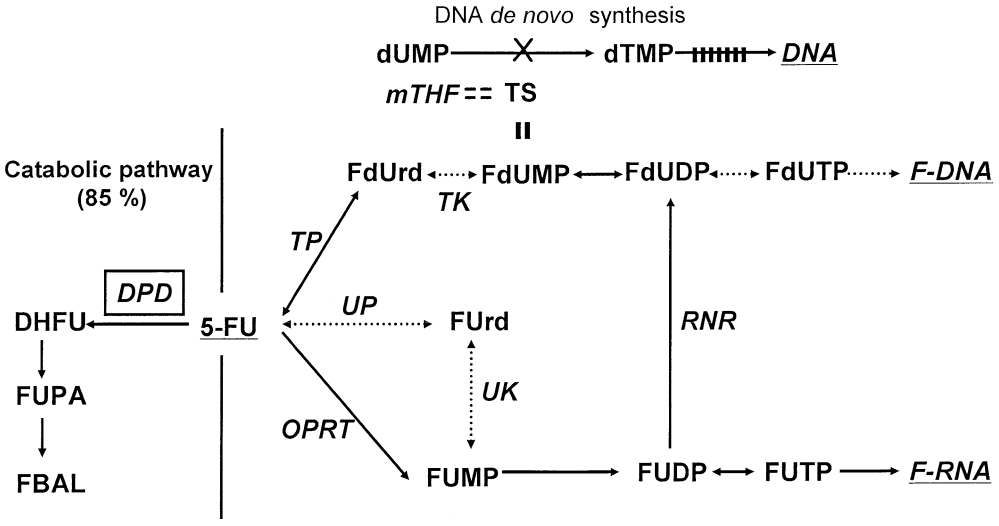

Fig. 1. Metabolic pathway of 5-fluorouracil (*5-FU*). *dUMP*, dUDP, and dTMP, deoxyuridine mono-, di-, and triphosphate, respectively; *mTHF*, 5,10-methylene tetrahydrofolate; *TS*, thymidylate synthase; *FdUrd*, fluorodeoxyuridine; *TK*, thymidine kinase; *TP*, thymidine phosphorylase; *DHFU*, dihydrofluorouracil; *FUPA*, fluoroureidopropionic acid; *FBAL*, α-fluoro-β-alanine; *UP*, uridine phosphorylase; *OPRT*, orotate phosphoribosyltransferase; *FUrd*, fluorouridine; *UK*, uridine kinase; *RNR*, ribonucleotide reductase; *FUMP*, *FUDP*, and FUTP, fluouridine mono-, di-, and triphosphate, respectively

Table 1. Classification of oral fluoropyrimidines

Drug	Mode of DPD inhibition	Remarks
DIFs		
UFT	Competitive (moderate)	Tegafur/uracil
Eniluracil/5-FU	Inactivation	–
S-1	Competitive (strong)	Tegafur/CDHP/Oxo[a]
Non-DIFs		
5-FU	None	–
Tegafur	None	5-FU prodrug
Doxifluridine	None	5-FU prodrug
Capecitabine	None	Doxifluridine prodrug

DIFs, dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidines; UFT, a mixed compound of tegafur and uracil at a molar ratio of 1:4; 5-FU, 5-fluorouracil; S1, 1 M tegafur – 0.4 M gimeracil – 1 M ostacil potassium; CDHP, gimeracil

[a] Tegafur/gimeracil/oteracil potassium

been reported (Table 2). The conformation of the *DPYD* gene (chromosome 1, p21–q22), its sequence,[17] and its crystal structure[18] have been identified; mutation/deletion of some base sequences has also been reported (Table 3). The exon 14-skipping mutation is well known,[19] but the relation between DPD deficiency and low DPD activity has not been fully explained.[20] Although reports on its promoter region have recently appeared,[21,22] independent groups showed different regions; hence future investigation is awaited. It is reported that DPD activity is low, appearing in about 3% of the Caucasian population;[23] it is even lower in Japan, with only two cases of identified DPD deficiency having been reported.[24,25] An ethnic difference is thus attracting interest.

Toxicity caused by 5-FU catabolites

It has been shown experimentally that a degradation product of 5-FU, α-fluoro-β-alanine (F-BAL), and its metabolites induce a certain toxicity.[26,27] Because the patterns of toxicity development clearly differ between DIF preparations and non-DIF preprations,[28–31] the possibility cannot be denied that control or inhibition of DPD decreases the degradation products and decreases toxicity.[32–35]

Relation between DPD and sensitivity to 5-FU

It is well known that thymidylate synthase (TS), a target enzyme of 5-FU, affects the sensitivity of 5-FU.[36–38] It is also reported that DPD determines 5-FU sensitivity.[39–44] Aboagye et al. noted that 83% of 5-FU exposed to tumor is degraded,[9] and it has been confirmed in clinical situations that DPD in tumors determines the effect of chemotherapy mainly based on 5-FU.[45,46] DPD, a rate-limiting enzyme for the degradation of 5-FU, is thought to be a strong factor in determining the effect of 5-FU, rather than TS. The possibility of employing DPD as a prognostic factor is also suggested,[46,47] although these results may be reflected in tumor progression.[48] It has been shown that DPD activity or expression in tumors differs from that in normal tissues depending on the type of carcinoma.[45,49–52] Larger-scale investigations and development of a method for inhibiting DPD according to the type of tumor are expected.

DPD inhibitory fluoropyrimidines

Because the pharmacokinetics and sensitivity of 5-FU are determined by DPD, stabilization of the pharmacokinetics of 5-FU and enhancement of its efficacy have been attempted by means of DPD inhibition. These fluoropyrimidines exhibiting a DPD inhibitory effect have recently been classified as DIFs.[4] It has also been revealed that their oral administration provides pharmacokinetics comparable to those seen with intravenous administration,[53,54] and it achieves a similar efficacy conveniently and safely.[28,29] Inhibition of DPD in tumors might be an effective strategy for overcoming the resistance of tumors with high DPD expression to 5-FU.[55–58]

Table 2. Adult cancer patients with DPD deficiency experiencing severe adverse drug reactions to 5-FU-based chemotherapy

Reference	Case	Treatment	Severe toxicities	DPD findings
Tuchman et al. (1985)	Female, 27 yr, breast cancer	CMF	Neutropenia, thrombocytopenia, diarrhea, stomatitis, encephalopathy	DPD not evaluated Familial thymine/uracil-urea
Diasio et al. (1988)	Female, 40 yr, breast cancer	CMF	Neutropenia, encephalopathy	DPD activity undetectable Elevated thymine/uracil in plasma/urine/CSF Familial DPD deficiency
Harris et al. (1991)	Female, 35 yr, breast cancer	CMF	Neutropenia, stomatitis, diarrhea, nausea/vomiting	DPD activity undetectable Familial DPD deficiency
Fleming et al. (1993)	Female, 65 yr, pancreatic cancer	5-FU cIV	Myelosuppression, mucositis	DPD not evaluated Elevated uracil in plasma
	Male, 37 yr, head and neck cancer	5-FU cIV/CDDP	Myelosuppression, mucositis	DPD not evaluated Elevated uracil in plasma
Houyau et al. (1993)	Female, 65 yr, cervical cancer	5-FU cIV/CDDP	Neutropenia, thrombocytopenia, mucositis, diarrhea, hand-foot syndrome	DPD activity severely decreased
Lyss et al. (1993)	Female, 59 yr, breast cancer	CMF	Leukopenia, thrombocytopenia, anemia, diarrhea, orthostatic syncope	DPD activity severely decreased
Stephan et al. (1995)	Female, 43 yr, cecal cancer	5-FU cIV/LV	Liver dysfunction, coma, seizure, nephropathy, CT finding compatible with 5-FU-related neurotoxicity	DPD activity severely decreased Elevated 5-FU in plasma/CSF
Takimoto et al. (1996)	Male, 50 yr, hepatocellular cancer	5-FU/LV/TXL	Encephalopathy	DPD activity severely decreased Elevated uracil in plasma/urine Familial DPD deficiency
Beuzeboc et al. (1996)	Female, 45 yr, breast cancer	5-FU/CPM/Mit	Neutropenia, thrombocytopenia, diarrhea	DPD activity severely decreased
Kouwaki et al. (1998)	Female, 57 yr, breast cancer	5′DFUR PO	Mucositis	DPD activity severely decreased Familial DPD deficiency
Johnson et al. (1999)	Male, 76 yr, skin cancer	5-FU cream	Neutropenia, thrombocytopenia, stomatitis, inflammatory colitis	DPD deficiency Elevated uracil in plasma/urine cDNA 165-bp deletion
Shehata et al. (1999)	Male, 57 yr, colon cancer	5-FU	Neutropenia, thrombocytopenia, mucositis, dermatitis, encephalopathy	DPD activity severely decreased
Inada et al. (1999)	Female, 44 yr, gastric cancer	5-FU/MMC	Granulocytopenia, nausea/vomiting	DPD activity severely decreased Elevated uracil in plasma/urine

CMF, cyclophosphamide/methotrexate/fluorouracil; 5-FU, 5-fluorouracil; cIV, continuous introutrously; CDDP, cis-diaminedichloroplatinum; LV, leucovorin; 5′DFUR, doxifluridine; MMC, mitomycin C; Mit, mitoxantrone; CT, computed tomography; DPD, dihydropyrimidine dehydrogenase; CSF, cerebrospinal fluid

Table 3. Reported *DPYD* gene mutations

Mutation	Nomenclature	Effect	Location
62G > A	DPYD*12	Arg21Glu	Exon 2
74A > G		His25Arg	Exon 2
85T > C	DPYD*9A, 9B	Cys29Arg	Exon 2
295–298 delT CAT	DPYD*7	Frameshift	Exon 4
496A > G		Met166Val	Exon 6
703C > T	DPYD*8	Arg235Try	Exon 7
812delT		Frameshift	Exon 8
1003G > T	DPYD*11	Val335Leu	Exon 10
1156G > T	DPYD*12	Glu386 > Stop	Exon 11
1601G > A	DPYD*4	Ser534Asp	Exon 13
1627A > G	DPYD*5, 2B	Ile543Val	Exon 13
1679T > G	DPYD*13	Ile560Ser	Exon 13
1714C > G		Leu572Val	Exon 13
1897 delC	DPYD*3	Frameshift	Exon 14
IVS14 + 1G > A	DPYD*2A, 2B	Del exon 14	Intron 14
2194G > A	DPYD*6	Val732Ile	Exon 18
2329G > T		Ala777Ser	Exon 19
2657G > A	DPYD*9B	Arg886His	Exon 21
2846A > T		Asp949Val	Exon 22
2921A > T		Asp974Val	Exon 23
2983G > T	DPYD*10	Val995Phe	Exon 23

Conclusions

The regulation mechanism for DPD itself has not been clarified. With the future progress of research, selection of drugs based on genetic pharmacological techniques and development of a drug that controls DPD more effectively are expected.

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