5-Fluorouracil (5-FU) was developed in 1957 based on the belief that substituting hydrogen with a fluorine on the pyrimidine ring might demonstrate tumor inhibition and that uracil may be used preferentially for nucleic acid biosynthesis in tumors (Grem, 1996). Although it was introduced over 30 years ago, 5-FU continues to be one of the most actively investigated anti-cancer drugs.

5-Fluorouracil is an anti-metabolite used in the treatment of carcinoma of the colon, rectum, breast, stomach, pancreas, and other malignancies (Cohen et al, 1993). The most common toxicities associated with 5-FU therapy, myelosuppression and stomatitis, are generally mild, predictable, and readily reversible upon discontinuation of the drug. Unfortunately, 5-FU has limited efficacy in advanced or metastatic disease and has not consistently improved tumor response or survival when administered alone or in combination with other anti-neoplastic agents (Ansfield et al, 1977; Lavin et al, 1980; Presant et al, 1984; Richards et al, 1986). Other approaches to enhance the efficacy of 5-FU include biochemical modulation with agents such as allopurinol (Howell et al, 1981), PALA (N-[phosphonacetyl]-L-aspartic acid; Erlichman et al, 1982), and leucovorin (Erlichman et al, 1988). Only use in combination with leucovorin has improved the efficacy, albeit modestly, of 5-FU (Erlichman et al, 1988). However, this biochemical modulation is not specific to tumors and generally also results in increased toxicity. Other approaches to increase the efficacy of 5-FU include the administration of 5-FU by prolonged continuous IV infusion (Lokich et al, 1989) and regional administration to the liver (Balch et al, 1987) and peritoneal cavity (Myers, 1984).

The limited anti-tumor activity of 5-FU may be due, in part, to its pharmacokinetics. Dihydropyrimidine dehydrogenase (DPD; uracil reductase, Enzyme Catalogue 1.3.1.2) is the first enzyme in a degradative pathway which rapidly reduces over 80% of systemic 5-FU (Heggie et al, 1987). Following IV administration of a single dose of 5-FU (400 to 600 mg/m²), the plasma half-life (t₁/₂) is approximately 6 to 20 minutes and varies substantially among patients (Grem, 1996). Within a few hours of administration, plasma concentrations fall below 0.13 μg/mL, the minimum concentration for in vitro cytotoxicity (Cohen et al, 1974). Greater than 80% of the 5-FU dose is ultimately converted to α-fluoro-β-alanine, a long-lasting catabolite (t₁/₂ of 33 hours in humans) that is not cytotoxic but was neurotoxic in cats (Heggie et al, 1987; Okeda et al, 1990). Only 10% of the 5-FU dose is excreted unchanged in urine. Patients deficient in DPD eliminate 5-FU with an extended t₁/₂ (3 hours or more) and excrete up to 90% of the 5-FU dose unchanged in urine (Fleming et al, 1993).

Dihydropyrimidine dehydrogenase is found in a variety of human tissues including kidney, liver, lung, intestinal mucosa, and solid tumors (Ho et al, 1986). In peripheral blood lymphocytes, DPD activity differs by at least 60-fold among patients and correlates directly with the rate of 5-FU elimination from plasma (Fleming et al, 1992). In addition, DPD activity varies with a circadian rhythm within individuals producing “mirror-image” variations in plasma 5-FU concentrations during continuous infusion (Harris et al, 1990). Varied amounts of DPD activity in intestinal mucosa (Spector et al, 1993) probably account for the...
highly variable oral bioavailability (0 to 77%) of 5-FU (Cohen et al, 1974; Christophidis et al, 1978; Finch et al, 1979; Abernethy et al, 1989). Results from in vitro human cell lines derived primarily from tumors of the gastrointestinal tract, breast, and head and neck have demonstrated a 100-fold variation in DPD activity (Beck et al, 1994). In these cell lines, DPD activity was found to be an independent factor directly related to 5-FU sensitivity.

The cytotoxic effects of 5-FU are likely the result of interference with deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis. Therefore, the effectiveness of 5-FU is probably at least partly dependent on cancer cells undergoing cellular division during exposure to the active metabolites of the drug. Because few cells are dividing at any given time and 5-FU is rapidly catabolized, most cancer cells are not likely to undergo division in the presence of active metabolites when 5-FU is administered by bolus IV injection. Results from multiple clinical studies indicate that prolonged systemic 5-FU exposure may improve the effectiveness of the drug (Milano et al, 1994; Hansen et al, 1989; Chang et al, 1989; Huan et al, 1989). A study in patients with squamous cell carcinoma of the head and neck demonstrated that 5-FU systemic exposure (as measured by area under the plasma concentration vs time curve [AUC]), but not dose, was significantly related to the extent of tumor response and survival (Milano et al, 1994). Studies of protracted continuous infusion of 5-FU have demonstrated tumor responses in patients with advanced colorectal cancer and advanced breast cancer that was refractory to 5-FU administered by bolus injection (Hansen et al, 1989; Chang et al, 1989; Huan et al, 1989). An alternative approach to prolonging systemic exposure to 5-FU, increasing exposure to active metabolites, and improving effectiveness would be to inhibit the catabolism of 5-FU by inactivation of DPD.

DPD inhibitors have been clinically studied and can produce a profound effect on the pharmacokinetics of 5-FU (Kindler et al, 2000). In both animals and humans, eniluracil, a potent DPD inhibitor, can result in approximately 100% bioavailability of orally administered 5-FU (Baccanari et al, 1993 and Baker et al, 1996, respectively). The terminal half-life of 5-FU is changed from 8 – 22 minutes when administered alone to 4.4 – 4.5 hours when given with eniluracil (Baker et al, 1996) and producing a prolonged exposure to 5-FU. The clinical implications of co-administration of 5-FU with eniluracil are under investigation.
REFERENCES


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