Biochemical and Clinical Pharmacology of 5-Fluorouracil

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The cellular and clinical pharmacology of fluoropyrimidines is characterized by marked interpatient variability in tumor response and patient tolerance. Understanding the metabolic pathways followed by 5-fluorouracil (5-FU) has

Introduction

In the 40 years since the introduction of 5-fluorouracil (5-FU), much has been learned about the metabolic pathways followed by this simple molecule, which differs from uracil only by the addition of a fluorine atom at the 5-position of the pyrimidine base. Figure 1 The complexity of the anabolic and catabolic pathways followed by 5-FU and their variability among tissue types, between normal and tumor tissues, and across individuals underlies the variety of outcomes observed following treatment of patients with 5-FU, both in tumor response and in toxicity to normal tissues. Understanding these metabolic pathways provides opportunities to optimize fluoropyrimidine chemotherapy by selecting those tumors most likely to respond to therapy as well as by screening individuals for an important genetic polymorphism that may increase the risk of developing severe 5-FU toxicity. In addition, new fluoropyrimidine modulators and prodrugs have been developed that may enhance the effectiveness of 5-FU or simplify its administration and improve its therapeutic index. This paper will briefly review the cellular and clinical pharmacology of 5-FU and discuss strategies for optimizing its effectiveness as an anticancer drug.

Cellular Determinants of Sensitivity to Fluoropyrimidines

The intracellular activation of 5-FU to its active nucleotide derivatives is depicted in Figure 2. A series of successive phosphorylation reactions leads to formation of 5-fluorodeoxyuridylate (5-FdUMP), 5-fluorodeoxyuridine triphosphate (5-FdUTP), or fluorouridine triphosphate (5-FUTP), the active forms of the drug. In most human tumors, the primary cytotoxic effect of 5-FU is believed to result from the binding of 5-FdUMP to thymidylate synthase (TS) thereby resulting in inhibition of DNA synthesis and induction of programmed cell death. The binding of 5-FdUMP to TS is optimized in the presence of 5,10 methylene tetrahydrofolate (5,10 CH₂THF) resulting in more sustained inhibition of TS. The conversion of 5-FU to 5-FUTP results in incorporation of this nucleotide into RNA, causing abnormal RNA processing, whereas the formation of the deoxynucleotide triphosphate (5-FdUTP) leads to misincorporation into DNA, resulting in DNA strand breaks. The extent to which any of these pathways predominates in human tumors is unknown and is likely to vary across tumor types and with different modes and doses of drug administration. Recent studies suggest, for example, that more prolonged exposure to low doses of 5-FU leads to cell death primarily via the TS-directed mechanism, whereas bolus administration of 5-FU results primarily in an RNA-mediated process of cell death. Key determinants of cellular sensitivity to 5-FU are summarized in Table 1. Among these, the level of TS expression in the tumor cells, the size of intracellular reduced folate pools, the intracellular activity of dihydropyrimidine dehydrogenase (DPD) and the activity of cell death pathways have been identified as important in determining response to fluoropyrimidine chemotherapy in patients with solid tumors. Thymidine phosphorylase activity may also be critically important in determining the effectiveness of a novel 5-FU prodrug, capecitabine, that relies on this enzyme for its intracellular activation.

Lenz and colleagues demonstrated that tumor response to 5-FU-containing chemotherapy and the survival of patients with gastric cancer was related to the level of TS expression in the primary tumor. Twenty of 57 evaluable patients responded to a regimen of continuous-infusion 5-FU, leucovorin, and cisplatin. The mean TS level in the tumors of responding patients was 2.6 ×10⁻³ whereas that in the tumors not responding to treatment was 6.8×10⁻³, a highly significant difference. Among patients with tumor TS mRNA levels less than the median value for the entire
group, 54% responded, whereas among those with tumor TS mRNA levels above the median, 17% responded. Perhaps more impressive was the observation that median survival of patients with low TS-expressing tumors was 43+ months compared with 6 months for patients whose tumors had TS mRNA values above the median. More recently, the same investigators evaluated tumoral TS and p53 expression in patients with metastatic colorectal cancer who were to receive a continuous infusion 5-FU regimen.[6,7] The response rate of tumors with TS levels below the median for the entire group was 52%, while that of tumors with high TS expression was 5%. [6] Eleven patients in this study failed to respond to therapy despite having tumors with TS levels below the median value, clearly indicating that TS level alone is not sufficient to predict response to fluoropyrimidine therapy for all patients. Mutation of p53 does not appear to be an independent predictor of response, though it may have prognostic significance.[7] In patients with head and neck cancer, Cheradame and colleagues were unable to demonstrate a relationship between tumor TS activity and response to 5-FU and cisplatin therapy. [8] However, a high degree of variability in intracellular reduced folate content among head and neck carcinomas as well as a correlation between reduced folate content and response to therapy was noted.[8] All responding patients had intratumoral reduced folate levels above the median for the entire population while 52% of nonresponding patients had levels below the median.

The intracellular content of 5-FU depends not only on drug delivery to the tumor and intracellular anabolism but on intracellular breakdown of 5-FU to inactive metabolites. The primary and rate-limiting enzyme in the catabolism of 5-FU is DPD, and results of recent studies suggest that the amount of DPD in tumor tissues may play a critical role in tumor response to 5-FU therapy. [9] Etienne et al prospectively studied 62 patients with head and neck cancer about to undergo induction chemotherapy with 5-FU/cisplatin or 5-FU/leucovorin/cisplatin. Pretreatment tumor biopsies were assayed for DPD and TS activity. No correlation was found between TS activity and response to therapy. However, low DPD activity, when normalized for normal tissue values, was correlated with a higher likelihood of tumor response. Similarly, Danenberg and colleagues measured DPD and TS gene expression in 33 colorectal tumors. [10] DPD mRNA levels varied by 80-fold among the tumors, and low DPD expression was predictive for improved clinical outcome; DPD mRNA level was less than 2.5 in all responding tumors. Median survival of patients whose tumor DPD level was greater than 2.5 was 5 months compared with 10 months for patients with tumor DPD levels less than 2.5. All patients who responded to 5-FU chemotherapy had tumors with low levels of both TS and DPD, whereas 21/22 nonresponders had high expression of either TS or DPD. Taken together, these results suggest that the likelihood of tumor response to fluoropyrimidine chemotherapy is based on multiple factors, including TS level, DPD level, and intratumoral reduced folate content, which may vary in importance across tumor types as well as among individuals with the same tumor type. For patients with colorectal cancer, low intratumoral levels of both TS and DPD appear to be important predictors of the likelihood of response to therapy. Ongoing clinical trials are evaluating whether these parameters can be used prospectively to select patients most likely to respond to fluoropyrimidine-based chemotherapy.

**Clinical Pharmacology of 5-Fluorouracil**

The clinical pharmacology of 5-FU is characterized by marked intra- and interpatient variability, nonlinear elimination kinetics, and erratic oral bioavailability. [11] Following an intravenous bolus dose of 500-600 mg/m², 5-FU disappears rapidly from plasma with a half-life of 8-14 minutes. As the administered dose increases, 5-FU displays saturable pharmacokinetics, ie, the plasma half-life increases, plasma clearance decreases, hepatic extraction decreases, and the area under the concentration-time curve (AUC) increases disproportionately. As a result, the plasma concentration achieved with any given dose is dependent on both the dose administered and the rate of infusion. The nonlinear kinetics displayed by 5-FU complicates dosage adjustment to achieve a desired target concentration, as both the desired target and the method of dose adjustment will be different with different schedules of drug administration. The clearance of 5-FU is much faster when given via continuous infusion than with bolus administration, allowing high cumulative doses of 5-FU to be safely administered. Nevertheless, the tolerable daily dose of 5-FU decreases with increasing infusion duration due to the schedule-dependent cytotoxicity of the drug. 5-FU is eliminated primarily by hepatic metabolism, with less than 5% of the drug excreted unchanged in the urine in normal individuals. Much of the variability in 5-FU pharmacokinetics has been attributed to intra- and interindividual variation in activity of DPD, the initial and rate-limiting enzyme in 5-FU catabolism (Figure 3). During continuous infusion of the drug, 5-FU plasma levels
vary throughout the day in a circadian pattern. Drug concentrations tend to be highest in the evening and lower in the early morning hours. Harris and colleagues have demonstrated an inverse relationship between DPD levels in peripheral blood lymphocytes and plasma 5-FU concentrations during continuous intravenous infusion of the drug.[12] The dose- and schedule-dependent pharmacokinetics of 5-FU can be attributed to saturation of DPD at high dose rates. Among cancer patients, DPD levels follow a gaussian distribution. Activity is not related to liver function, race, or age but tends to be approximately 15% lower in women than in men.[13] Women with breast cancer have been found to have even lower mean values for DPD activity and 5.8% of a population of 360 breast cancer patients were considered to be DPD deficient, a situation that predisposes to severe 5-FU toxicity following administration of standard doses of the drug.[14] Although DPD activity in normal tissues varies over a 10- to 20-fold range, it has not yet been possible to demonstrate a strong relationship between pretreatment DPD level and 5-FU clearance or risk of toxicity.[13,15] It is clear, however, that individuals who have a homozygous deficiency in DPD are at high-risk for severe 5-FU toxicity due to a marked reduction in 5-FU clearance.[16,17] Although further studies are necessary to determine whether pretreatment assessment of DPD activity can be used reliably to guide 5-FU dosing, it appears that individuals with DPD levels at or below 0.100 nmol/min/mg protein (2% to 3% of the population) are at high risk of severe 5-FU toxicity and should be considered for dose reduction or alternative therapy.

Whether 5-FU plasma concentrations can be used to individualize dosing remains controversial. In view of the complex intracellular metabolism required for drug activation and the variety of intracellular determinants of drug effect, it would be surprising if plasma concentration alone were predictive of toxicity or response to therapy. Several investigators have, however, demonstrated a link between 5-FU systemic exposure and risk of toxicity. In head and neck cancer patients, systemic 5-FU exposure has been linked to the risk of severe toxicity, and prospective dose adjustment to achieve a target AUC has been used successfully to minimize this risk.[18] In an extension of these studies, Milano et al examined the relationship between systemic exposure to 5-FU, tumor response, and survival in patients with head and neck cancer treated with cisplatin plus 5-FU administered as a 5-day continuous infusion at a dose of 1 g/m²/day.[19] In a multivariate analysis of prognostic factors, tumor stage and 5-FU AUC were significantly associated with prolonged survival whereas 5-FU dose was not predictive of the likelihood of response or duration of survival. An optimal threshold 5-FU AUC of 29,000 ng/mL•h was demonstrated in that patients achieving drug exposure above this value had the longest survival. These data suggest that adjusting 5-FU doses to achieve optimal systemic exposure might enhance the efficacy of 5-FU-based therapy in head and neck cancer patients, though the practical feasibility of doing so has yet to be established.

Similar approaches have recently been reported in patients with metastatic colorectal cancer. Pharmacokinetic studies involving patients treated with weekly 8-hour infusions of 5-FU demonstrated a relationship between plasma levels greater than 3,000 µg/mL and risk of severe toxicity, and a therapeutic range of 2,000-3,000 µg/mL was proposed to minimize toxicity while optimizing chances for tumor response.[20] In a multicenter phase II study of 152 metastatic colorectal cancer patients, the 5-FU dose was adjusted weekly in an attempt to achieve plasma concentrations within the desired range.[21] The 5-FU dose necessary to achieve the desired plasma concentration was highly variable, ranging from 950 to 3,695 mg/m², and the therapeutic range was achieved in 143 of 152 patients. Toxicity was generally mild and limited to grade 1-2 diarrhea and hand-foot syndrome. Treatment efficacy was evaluated in patients who had 5-FU plasma concentrations within the therapeutic range for at least 2 months. Of 117 patients with measurable disease there were 18 complete and 48 partial responses. Median survival of all 152 patients was 19 months. Although these results are impressive, it is difficult to draw definitive conclusions from a noncontrolled phase II study. Indeed, the average weekly 5-FU dose of 1,803 ± 386 mg/m²/wk administered in this study is lower than that commonly used with weekly 24-hour infusion regimens (2,600 mg/m²/wk), which are reported to produce similar response rates. Nevertheless, these results again highlight the enormous interpatient variability in 5-FU pharmacokinetics and suggest that efforts to minimize such variability can reduce 5-FU-associated toxicity.

**Optimizing Fluoropyrimidine Chemotherapy**

Two key strategies for optimizing use of fluoropyrimidines emerge from understanding the cellular and clinical pharmacology of these agents. First, it now seems possible to select those tumors most likely to respond to fluoropyrimidine therapy by analyzing the expression of key genes within the tumor tissue that influence response. Among these, TS and DPD appear to be important...
determinants of treatment outcome, particularly in colorectal cancer patients. Without modifying the 5-FU dose or schedule, better patient selection is likely to improve response rates from the range of 20% to 25% to the range of 40% to 50% and to improve the survival duration. The challenge is to develop assay technologies that will permit determination of enzyme levels in the small amounts of tumor that can be obtained with minimally invasive techniques and/or that will permit reliable assessment of gene expression using paraffin-embedded tissue. Analysis of enzyme expression in tumor tissue might also facilitate selection of the optimal fluoropyrimidine for use in a particular clinical situation. Thus, tumors with high levels of DPD might best be treated with 5-FU in combination with a DPD inhibitor. Those tumors that overexpress thymidine phosphorylase would be excellent candidates for therapy with capecitabine, a new fluoropyrimidine that is selectively activated in tissues with high TP activity.[22] Tumors with high TS expression might be expected to be relatively resistant to all fluoropyrimidines and thus require a different class of agents, such as topoisomerase I inhibitors, for initial therapy. Strategies such as these need to be validated in prospective clinical trials, but the potential clearly exists to optimize therapy by understanding the fluoropyrimidine phenotype of the tumor.

A second strategy that may be useful in optimizing fluoropyrimidine therapy is attempting to minimize the variability in 5-FU elimination. The variability in 5-FU pharmacokinetics that exists both within and between patients leads to a great deal of variability in tolerance to the drug, makes oral dosing impractical due to unpredictable bioavailability, and complicates dose adjustment strategies due to the non-linear relationship between dose and AUC. If such strategies are indeed useful in optimizing the therapeutic index of 5-FU, then developing methods to more reliably predict relationships between dose and plasma concentration will be extremely important for the future. Because most of the variability in 5-FU kinetics is due to variation in DPD activity within and between patients, a logical treatment strategy is to combine 5-FU with a specific DPD inhibitor. One such agent is eniluracil, a specific and irreversible inactivator of DPD.[23] Combinations of eniluracil and 5-FU have been studied using 5-day and 28-day schedules of 5-FU.[24,25] Coadministration of the two drugs makes 5-FU 100% orally bioavailable due to inhibition of DPD activity in the gut wall and liver.[26] Thus, protracted exposure to 5-FU can be achieved by chronic oral dosing and without the need for indwelling catheters and infusion pumps. Perhaps more importantly, in the presence of eniluracil, 5-FU displays predictable, linear pharmacokinetics thereby facilitating dosage adjustment to achieve a target concentration. In addition, elimination of 5-FU metabolites that results from use of eniluracil may potentially enhance the therapeutic activity of 5-FU, and DPD inhibition within tumor tissue is likely to enhance tumor sensitivity to 5-FU as well.[27] Because 5-FU clearance decreases and half-life is prolonged in the presence of eniluracil, the doses of 5-FU that can be safely administered with this agent are markedly reduced compared with standard doses. Nevertheless, the combination 5-FU and eniluracil appears to have activity in treatment of patients with advanced colorectal cancer.[28,29] Thus, the strategy of using a DPD inhibitor in combination with 5-FU to minimize the variability in 5-FU pharmacology appears to have promise and is being pursued in randomized clinical trials in several tumor types.

Summary

The cellular and clinical pharmacology of fluoropyrimidines is characterized by marked interpatient variability in tumor response and patient tolerance. Understanding the metabolic pathways followed by 5-FU has led to new strategies to optimize therapy with these important agents. The fluoropyrimidine phenotype of tumor cells can be used to determine whether therapy with these agents is appropriate and, if so, whether one fluoropyrimidine may offer a particular advantage over another. Combining a DPD inhibitor with 5-FU offers the potential to minimize pharmacokinetic variability and, in that way, to improve oral bioavailability, facilitate dosage adjustment to achieve desired concentrations, and increase the likelihood of tumor response while minimizing the risk of severe toxicity to individual patients.

References:
2. Sobrero AF, Aschele C, Bertino JR: Fluorouracil in colorectal cancer - a tale of two drugs:


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