Schedule Dependency of 5-Fluorouracil

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5-Fluorouracil (5-FU) is cell-cycle specific for its cytotoxicity and has a pharmacokinetic profile characterized by a short, single-dose half-life of 10 to 20 minutes in plasma. Efforts to maximize its clinical efficacy have been

Introduction

Schedule dependency for fluorinated pyrimidine-based therapy has been an issue since Ansfield's early investigations.[1] Until very recently, the pharmacologic armamentarium against colorectal cancer was extremely limited. Because single-agent 5-fluorouracil (5-FU) has been the mainstay in treatment of this disease, much of the clinical study of this drug has occurred in the setting of colorectal cancer. Consequently, clinical trials of 5-FU-based regimens for disseminated colorectal cancer have focused on biochemical modulation and schedule dependency as a means of enhancing therapeutic efficacy.

5-FU Pharmacokinetics

Mechanism of Action

A major mechanism of 5-FU action is inhibition of thymidylate synthase activity by competitive binding of F-dUMP (5-fluorodeoxyuridine monophosphate) with the dUMP binding site on the enzyme molecule, thus inhibiting the rate-limiting step for thymidine and, therefore, DNA synthesis. This process is cell-cycle (S-phase) specific, making drug activity irregular against the sensitive portion of the tumor cell population. Potential for cytotoxic activity is further impaired by the rapid catabolic rate for the drug, reflected in the short plasma half-life of 10 to 20 minutes, when given as a bolus injection.[2,3]

5-FU has also been shown experimentally and in clinical trials to function as a radiation sensitizer.[4] In this setting, short half-life, overlapping toxicities, and enhanced toxicity with the addition of modulators have additional therapeutic implications. Furthermore, in the disseminated disease setting, where palliation is a goal in addition to enhancement of response rates, time-to-progression, and survival, the issue of type and degree of toxicity is an important one.

Dose Intensity

To increase tumor cell kill and response rates in the disseminated disease setting and to project the best regimen for eradication of micrometastases in the adjuvant setting, dose intensity may be important in determining the schedule for optimal drug delivery. Dose intensity is defined as the amount of drug delivered per unit of time, typically reported as milligrams per square meter per week or per 28 days, regardless of the schedule used.[5] A dose-intense regimen may or may not be associated with high peak drug levels. Continuous administration of chemotherapeutic regimens may be quite dose-intensive but may also be associated with lower peak concentrations.[6] Acceptability of dose-intense regimens is dependent on the degree of toxicity encountered, which, in turn, may depend on whether the goal of therapy is palliative or curative. Drug metabolism and catabolism also need to be taken into account in the design of dose-intense chemotherapy regimens.

For the standard Mayo daily times 5, once-a-month regimen of 5-FU plus low-dose calcium folinate being used in both adjuvant and disseminated settings, a 5-FU dose of 375 to 425 mg /m² yields a 28-day dose of 1,900 to 2,100 mg/m². For the Roswell Park weekly regimen of 500 mg/m² of 5-FU with high-dose calcium folinate administered for 6 of 8 weeks in the same settings, a 28-day dose of 1,500 mg/m² is received. For continuous infusions of 5-FU, 200 to 300 mg/m²/day, with or without calcium folinate, the comparable 28-day dose is 5,600 to 8,400 mg/m², and for the intermittent, weekly, high-dose 24-hour infusion of 2,600 mg/m², the 28-day dose is 10,400 mg/m². These doses are contingent on no dose reduction, so the additional question is raised of what relative percentage of patients receiving each regimen will experience a degree of toxicity requiring dose reduction.
In the face of an obvious dose-intensity advantage conferred by the infusional regimens, it is noteworthy that we fail to see comparable differences in activity. Is the explanation that there is a maximum dose intensity of 5-FU beyond which no further clinical activity is achieved? Dose intensity is based on area under the concentration-time curve for plasma pharmacokinetics. As such, is the constant level of drug for diffusion into the cell, which characterizes the infusional regimens, balanced by ternary complex formation and degree of intracellular polyglutamylation of bolus regimens administered with calcium folinate? Or, do other factors, such as intratumor levels of thymidylate synthase or mutations of oncogenes and tumor suppressor genes, ultimately override both dose intensity and biochemical modulation in determination of response?

Biochemical Modulation
The value of altering the schedule of or biochemically modulating 5-FU was tested in phase I and II trials designed to identify intravenous and oral doses of calcium folinate for addition to continuous infusion 5-FU.[7,8] Toxicities encountered predominantly plantar-palmar erythrodysesthesia (hand-foot syndrome) and stomatitis were of higher grade and earlier onset than those that occurred with single-agent 5-FU, resulting in a net reduction in dose intensity of 5-FU. The question remained, however, about the relative roles of biochemical modulation vs schedule dependency. To answer this question, the Southwest Oncology Group (SWOG) [9] conducted a phase II trial in which more than 600 patients were randomized over a 3-year period to paired regimens of bolus (daily times 5, once a month; weekly) and infusional (protracted low-dose; weekly high-dose) 5-FU, with and without biochemical modulators (calcium folinate, PALA [N-phosphoroacetyl-L-aspartic acid]). None of the regimens tested demonstrated a statistical superiority for either response or survival. Response rates ranged from 15% to 29%; median survival ranged from 11 to 15 months.

In a subsequent phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG), investigators randomly assigned more than 1,100 patients to five treatment arms of 5-FU given by weekly bolus or weekly infusion, with or without modulation (intravenous or oral calcium folinate, PALA, or a-interferon).[10] Again, no regimen demonstrated statistically superior activity over the others. Median survival was nearly identical to that in the Southwest Oncology Group trial, ranging from 13 to 15 months.

Toxicity
In both of these trials, the infusion arms demonstrated a lower percentage of grades 3 and 4 toxicity. Furthermore, the pattern of dominant toxicities, ie, stomatitis and hand-foot syndrome, allows for earlier intervention with careful patient observation, thus avoiding higher toxicity grades with consequent extensive dose reduction. Given the inherent increased dose and the less frequent dose reduction encountered, the dose-intensity advantage persists for these arms. Though not reaching statistical significance, in the SWOG trial a trend toward response and survival benefit was seen for the single-agent 5-FU infusion arms (Figure 1, Figure 2, and Figure 3).

Meta-Analysis
The Meta-Analysis Group in Cancer examined data from seven international randomized trials that included comparable bolus and infusion regimens, with or without calcium folinate modulation.[11] Pooled data demonstrated a statistically significant response advantage for continuous-infusion 5-FU compared with bolus 5-FU (Table 1). A small survival advantage was also detected for the infusion treatment (Table 2). Differences were less obvious when both methods of 5-FU administration were modulated by calcium folinate. As expected, toxicity patterns differed between bolus and infusion regimens.

Cost Comparisons
In addition to response, survival, and toxicity analyses, the issue of comparative costs has become important in today’s increasingly controlled medical market. A major component of cost differential between these two modes of drug administration is the up-front cost of catheter placement. When amortized over the course of treatment, this cost, along with pump rental charges, tends to lessen the cost differences over time, particularly for those patients who respond to therapy. The expense of calcium folinate used with the bolus regimens may also serve to offset differences when compared with single-agent infusion regimens.[12,13] Treatment of toxicity related to the different therapeutic regimens also needs to be included in this analysis: hospitalization for dehydration and neutropenic sepsis is more commonly required for calcium folinate-modulated bolus 5-FU schedules, whereas the expense of treating catheter infections and thromboses needs to be figured into the analyses for infusional regimens. These
analyses are difficult to accurately perform, as regional differences in the cost of medical services also enter the equation. The Meta-Analysis Group in Cancer is currently undertaking this task for the patients included in the report cited above.

**Ongoing Studies**

**Current Clinical Trials**

Based on observations of response and toxicity patterns from their previous trials, SWOG and ECOG have joined in a phase III trial comparing protracted continuous infusion of 5-FU 300 mg/m²/day for 28 days followed by a 1-week rest, with weekly high-dose infusion at 2,600 mg/m² over 24 hours (Southwest Oncology Group 9420, Cynthia Gail Leichman, MD, principal investigator). The question of dose intensity remains essential to this trial: Can it be maximized to therapeutic benefit, or is there a threshold beyond which no gain is seen? SWOG is conducting a correlative trial of tumor expression of thymidylate synthase to correlate with response in an effort to address dose vs tumor biology impact on this issue.

Issues of convenience and cost are also linked to the outcome of this trial. Patient acceptance of the ambulatory infusion device for 1 day per week is likely to be much higher, and the per patient cost less, than for continuous use of the device. Also, the intermittent schedule allows more patients to be serviced by a single reusable pump, which should ultimately bring down costs. ECOG is conducting a cost analysis as a companion study to this trial.

The outcome of this trial may also have implications for combination and multimodality therapies. Prolonged, continuous-infusion 5-FU may have therapeutic advantages for use with radiation, and has been used in this setting in the treatment of esophagus,[14,15] head and neck,[16,17] breast,[18] and rectal cancers,[19] alone or in combination with other chemotherapeutic agents (cisplatin [Platinol], mitomycin-C [Mutamycin]). High-dose weekly infusion 5-FU has been combined with biochemical modulators in addition to PALA (hydroxyurea [Hydrea],[20] calcium folinate,[21,22] and interferon[23]) as well as with other chemotherapy agents (cisplatin,[24] etoposide [VePesid],[25] paclitaxel [Taxol],[26] and oxaliplatin[27]) and has also been used in a variety of tumor types.

As with low-dose continuous-infusion 5-FU, the question of additional clinical benefit from biochemical modulation of high-dose 5-FU infusion via addition of calcium folinate has been addressed in a number of phase II and pilot trials reported recently. Doses of calcium folinate ranging from 100 to 500 mg/m² have been examined. Toxicity profiles, although generally tolerable, include an incidence of grades 3 and 4 diarrhea that is significantly higher than previously observed with single-agent 5-FU and more similar to that of the weekly bolus 5-FU with high-dose calcium folinate.

Response rates of 40% to 42% were achieved in chemotherapy-naive patients and 14% to 23% in patients with prior fluoropyrimidine exposure. Although the former figures, largely from single-institution trials, are somewhat higher than the response rate of the previously cited randomized trials, the response rates for previously treated patients are consistent with those achieved by low-dose continuous-infusion 5-FU. No trial has yet been reported that compares single-agent, high-dose 5-FU infusion with a comparable calcium folinate-modulated regimen to determine if the added toxicity is accompanied by a proportional increase in clinical response.

**Current Adjuvant Trials**

In the adjuvant treatment of stage III colon cancer, an investigational arm of continuous-infusion 5-FU in conjunction with levamisole (Ergamisol) is being compared with daily times 5, once-a-month bolus 5-FU plus low-dose calcium folinate and levamisole, as the standard arm (selected from the previous Intergroup adjuvant colon cancer trial, INT 0089) in INT 0136.

For stages II and III rectal cancer, INT 0144 compares three regimens, two of which employ a component of 5-FU infusion therapy in conjunction with standard pelvic radiation scheduled in a sandwich fashion. Based on the results of North Central Cancer Treatment Group (NCCTG) 86-47-51, which demonstrated a survival advantage for patients receiving infusional 5-FU throughout pelvic radiation, the standard arm of this protocol administers bolus 5-FU for two cycles on a daily times 5 schedule. This is followed by radiation with continuous-infusion 5-FU and a subsequent two cycles of bolus 5-FU. The second arm utilizes the infusion regimen throughout, and the third arm gives the double-modulated 5-FU bolus regimen (calcium folinate and levamisole) throughout.

**Future Directions: Oral Chemotherapy Regimens**

Whether or not the current generation of adjuvant trials in colorectal cancer demonstrates a survival
advantage or preferable toxicity profile for infusion regimens compared with the bolus regimens, the next generation of adjuvant trials will likely contain an oral fluoropyrimidine regimen as an investigational arm. The National Surgical Adjuvant Breast and Bowel Project has recently completed such a trial, C-06, in which standard weekly bolus 5-FU with high-dose calcium folinate is being compared with UFT (uracil and tegafur in a 4:1 molar ratio) plus oral calcium folinate (Orzel). The rationale for this approach, in addition to double modulation of the 5-FU, is that split daily dosing of this compound in phase I trials has demonstrated a pharmacokinetic profile similar to that of continuous-infusion 5-FU. These trials have demonstrated a range and grade of toxicity comparable to that of standard intravenous regimens. Certainly, in the setting of intact gastrointestinal function, this approach represents a convenience advantage for patients. Whether it represents a cost advantage remains to be determined.

References:


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