Phase I Study of Eniluracil, a Dihydropyrimidine Dehydrogenase Inactivator, and Oral 5-Fluorouracil with Radiation Therapy in Patients with Recurrent or Advanced Head and Neck Cancer

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ABSTRACT

5-Fluorouracil (5-FU) is an effective enhancer of radiation therapy (RT) in head and neck cancers. Due to rapid, predominantly hepatic metabolism by dihydropyrimidine dehydrogenase (DPD) and suggested clinical benefit from prolonged drug exposure, 5-FU is commonly given by continuous infusion. Eniluracil is a novel DPD-inactivator designed to prolong the half-life of 5-FU and provide sustained plasma concentrations of 5-FU with oral dosing. We conducted a Phase I study of the safety and efficacy of eniluracil given with oral 5-FU in patients receiving concurrent RT for recurrent or advanced squamous cell carcinomas of the head and neck.

Thirteen patients with recurrent, metastatic, or high-risk (defined as an expected 2-year survival rate of <10%) head and neck cancer were enrolled and treated with concomitant chemoradiotherapy on an every-other-week schedule. Eniluracil at a fixed dose [20 mg twice a day (BID)] was given for 7 consecutive days (days 1–7). 5-FU and RT were given on 5 consecutive days (days 2–6). One patient was treated with once-daily RT (2.0 Gy fractions). The remaining patients received hyperfractionated RT (1.5-Gy fractions BID). The initial dose of 5-FU was 2.5 mg/m² given BID. Dose escalation in patient cohorts was scheduled at 2.5-mg/m² increments, with intrapatient dose escalation permitted.

Lymphocyte DPD activity and serum 5-FU and uracil concentrations were monitored during two cycles.

DPD activity was completely or nearly completely inactivated in all patients. Sustained, presumed therapeutic concentrations of 5-FU were observed at a dose of 5.0 mg/m² given BID. Cumulative dose-limiting myelosuppression (both neutropenia and thrombocytopenia) was observed during the fourth and fifth cycles following administration of 5.0 mg/m² 5-FU BID. One patient died of neutropenic sepsis during cycle 4. Other late cycle toxicities included diarrhea, fatigue, and mucositis. Grade 3 mucositis was observed in 4 patients, but no grade 4 mucositis or grade 3 or 4 dermatitis was observed. A second patient death occurred during cycle 1 of treatment. No specific cause of death was identified. The study was subsequently discontinued.

Cumulative myelosuppression was the significant dose-limiting toxicity of oral 5-FU given with the DPD-inactivator eniluracil on an every-other-week schedule. Clinical radiation sensitization was not observed, based on the absence of dose-limiting mucositis and dermatitis. Alternative dosing schedules need to be examined to determine the most appropriate use of eniluracil and 5-FU as radiation enhancers.

INTRODUCTION

Concomitant chemoradiotherapy has been investigated for the last 30 years and has recently become an accepted treatment option in patients with locoregionally advanced head and neck cancers. Numerous randomized studies conducted over this time period have demonstrated improved outcomes based on preservation of organ function and survival (1). Recent meta-analyses have confirmed these conclusions (2, 3). Many chemotherapeutic agents have been used as radiation sensitizers in these studies, including platinum compounds, bleomycin, mitomycin, and antimetabolites such as methotrexate and 5-FU. Our focus has been on a core chemotheraphy regimen consisting of 5-FU and hydroxyurea given with daily or twice-daily radiation (4–10). The concomitant chemoradiotherapy was given in split courses for 5 consecutive days on an every-other-week schedule. This regimen has been well tolerated, has allowed organ preservation, and has produced high response and survival rates in previously untreated patients. High response rates with potential for cure have also been demonstrated in previously irradiated patients.
patients (11). The addition of other chemotherapeutic drugs to this core regimen has been studied (12, 13).

5-FU has a short half-life (8–22 min) resulting from rapid metabolism in the liver and other tissues by the enzyme DPD (14, 15). To overcome the short plasma half-life of 5-FU and maximize exposure to the drug during the times encompassing radiation exposure, 5-FU is often given by continuous infusion. This dosing regimen, therefore, requires patient hospitalization or the use of expensive and cumbersome infusion pumps as well as indwelling venous access devices. New approaches to the use of 5-FU have focused on modification of 5-FU pharmacokinetics through inhibition of metabolism. Eniluracil is an experimental drug that is specifically designed to inactivate DPD and prolong the half-life of 5-FU (16). In clinical trials, eniluracil has been shown to increase the half-life of 5-FU by 8–30-fold (from 8–22 min to 4.5 ± 1.6 h). The area under the concentration-time curve for 5-day continuous dosing of 25 mg/m² 5-FU given with eniluracil was similar to the area under the concentration-time curve for the 1000-mg/m² dose of 5-FU given by continuous infusion for 5 consecutive days. Additionally, eniluracil increases the oral bioavailability of 5-FU to ∼100% (17). In the absence of DPD inactivation, the oral bioavailability of 5-FU is highly variable, ranging from 0 to 80% (18). This variability in bioavailability is felt to be due to significant first-pass metabolism by DPD in both the gastrointestinal mucosa and the liver (19).

Inactivation of DPD may also provide therapeutic benefit beyond its effect on the half-life of 5-FU. Evidence exists to suggest that intratumor levels of DPD correlate inversely with response to 5-FU (20, 21). Thus, it is reasonable to hypothesize that eniluracil, through inactivation of DPD at the tumor level, may also enhance efficacy of 5-FU without significantly increasing toxicity.

We, therefore, undertook a Phase I study combining eniluracil and oral 5-FU and hydroxyurea with RT in patients with recurrent or high-risk cancers of the head and neck to determine the feasibility and safety of an all oral dosing of our FHX regimen.

PATIENTS AND METHODS

Eligibility

Patients with histologically confirmed malignant oral or laryngeal neoplasm of the head and neck requiring regional RT were considered eligible for enrollment. Prior RT and/or chemotherapy and/or surgery did not preclude enrollment, consistent with our previous Phase I studies (10, 12). Patients with metastatic disease were eligible if the predominant site of disease and associated symptoms required local treatment with RT in the head and neck region. Those patients with previously untreated disease were eligible if they had unresectable disease and an estimated 2-year survival of <10%. Measurable disease was not required. A performance status (Cancer and Leukemia Group B) of ≥2 was required. The ability to swallow and retain oral medications was required. The following laboratory parameters were required at study entry: WBC count of ≥3,000/μl, platelet count of ≥100,000/μl, and estimated creatinine clearance of ≥50 ml/min (using the Cockcroft-Gault formula). Written informed consent was obtained before the initiation of treatment.

All patients were evaluated by a surgical, medical, and radiation oncologist before trial entry. Stage, optimal standard therapy, and eligibility for the protocol were determined jointly. Uniform staging and preparatory procedures included: a computed tomographic scan of the head and neck, brain, and lungs; a bone scan; and a dental evaluation. A gastrostomy tube for supplemental nutrition and an implanted central venous access device were strongly recommended. The protocol was approved by the institutional review boards of the participating institutions.

RT Guidelines

All patients were simulated prior to the start of RT with an appropriate immobilization device. Appropriate field sizes to treat gross disease and areas of potential microscopic disease were determined at the time of simulation. Initial opposed lateral fields were used to treat the primary disease and the neck. The supraclavicular fossae, when indicated, were treated with a separate field. A posterior cord block or midline block was used on the lateral or supraclavicular fields to minimize the chance of overlap on the spinal cord. Each cycle of RT consisted of 5 days of consecutive treatment. The first patient enrolled received once-daily RT (200-cGy fractions) for a total of 70 Gy. All subsequent patients received twice-daily RT (150-cGy fractions).

Previously unirradiated patients were treated as follows. Anterior neck doses for microscopic disease were 50–60 Gy. Boosts were given to the primary areas and areas of gross disease after appropriate field reductions, to a total dose of 66–72 Gy for small-volume (≤4 cm) disease or 70–75 Gy for bulkier (≥4 cm) disease. The dose delivered to the supraclavicular fossae was 44–50 Gy for microscopic disease. For gross disease, a total of 66–74 Gy was delivered. The dose to the posterior neck was 45–60 Gy for microscopic disease and 66–74 Gy for gross disease. Electrons were used to boost the posterior neck to minimize the dose to the spinal cord to ≤45 Gy in those patients treated once daily and to ≤40 Gy in those treated twice a day.

Previously treated patients were treated more heterogeneously, based on the constraints of prior therapy. In general, gross disease received 7100–7500 cGy. Areas considered at risk for microscopic disease received 4500–6000 cGy.

Chemotherapy

The patients were scheduled to receive four to five cycles of concomitant chemoradiotherapy, each lasting 14 days. A fixed 20-mg BID dose of eniluracil was administered on days 1–7 of the treatment week at all dose levels (14 total doses per cycle). 5-FU was administered twice a day on days 2–6 of each treatment cycle. No therapy was given on days 8 to 14. The treatment scheme is given in Fig. 1.

Supportive Care

All patients were seen by a dietitian in the hospital and were begun on supplemental feedings via gastrostomy tube when their oral caloric intake became inadequate. Daily hydration with 1000–2000 ml of normal saline was given at home or on an outpatient basis for 6 days after chemotherapy. Electro-
lytes were substituted as necessary. Good oral hygiene was maintained using a saline mouth rinse and a combination of lidocaine, diphenhydramine, and sodium bicarbonate mouth rinse at least four times a day. Oral antifungal prophylaxis with a nystatin (100,000 units/ml) 5-ml rinse and swallow was also initiated. Patients who were unable to tolerate nystatin and those who developed candidiasis (other than very mild oral thrush) were treated with fluconazole. Skin care in the radiation field was aggressive. A water-based, aloe-containing gel was applied after the final daily treatment and removed before the first daily treatment. A hydrogel barrier dressing was applied after each RT treatment when moist desquamation occurred. Patients were seen at least once during their off-treatment week in the outpatient clinic.

**Dose Escalation**

Patients were treated in cohorts of at least three to six individuals. Beginning with a dose of 2.5 mg/m² BID, dose escalation of 5-FU was planned at 2.5 mg/m² intervals. Decisions to escalate the dose of 5-FU were based upon acute toxicities in cycles 1 and 2. If no more than one patient developed DLT, the 5-FU dose was increased in the next patient cohort. If two patients developed toxicity at a given dose level, an additional three patients were treated, for a total of at least six. If three patients experienced DLT, that dose level was considered the MTD. Intrapatient dose escalation was permitted if the patient experienced no acute toxicities (grade of 1-2) after two cycles at a particular dose level. Delayed toxicities, those in cycles 3-5, also influenced decisions to proceed with dose escalation. For final determination of MTD, all cycles were evaluated. The RPTD was defined as one dose level below the MTD. Following determination of MTD, hydroxyurea was scheduled to be added to the regimen on a twice-daily schedule.

**DLT**

DLT was defined as follows: hematological toxicity of grade 4 for >4 days or persisting on day 1 of the next cycle or development of a neutropenic fever; mucositis or dermatitis of grade 4 not resolved to a grade of ≤3 on day 1 of the next cycle; or any other grade 3 toxicity (except nausea/vomiting and alopecia). Failure to receive the chemotherapy in full dose within 24 h of the scheduled time during the first two cycles was also considered dose limiting. Only DLTs occurring during the first two cycles were considered essential for dose escalation purposes. Cumulative toxicities (those experienced in later cycles) were, however, weighed in decisions to escalate dose and in determination of RPTD.

**Dose Modifications**

Dose modifications were made according to the following guidelines: (a) for grade 4 mucositis, dermatitis, or diarrhea exceeding 7 days duration or persisting on day 1 of a cycle, 5-FU was decreased by two dose levels (50% for dose levels 1 and 2); (b) for a WBC count of 1,000–1,900/µl or a platelet count of 50,000–74,000/µl on day 1 of any cycle, 5-FU was decreased by one dose level (25% on dose level 1); and (c) for a WBC count of <1,000/µl or a platelet count of <50,000/µl on day 1 of any cycle, 5-FU was decreased by two dose levels, and radiation was continued. A cycle could be postponed for 1 week in the presence of a fever of >38°C or other clinically apparent infection or at the discretion of the treating physician. No treatment delays were permitted for dermatitis, mucositis, or diarrhea. Patients were removed from the study if they became unable to take the medications p.o.

**Study End Points**

The primary end point of the study was determination of toxicity and definition of RPTD. Response rate, time to progression, and survival were secondary end points. The ability to obtain radiosensitizing plasma 5-FU concentrations was also evaluated as part of this study. Patients with measurable disease were evaluable for response only after completion of all intended chemotherapy and RT. CR was defined as the complete disappearance of all detectable disease. Surgical or biopsy confirmation was attempted in patients determined to have clinical or radiological CRs. Partial response was defined as a reduction by at least 50% of the products of the longest perpendicular diameters of measurable tumor lesions. At the same time, no growth of other lesions or appearance of new lesions was permitted.

Patients with stable disease had a decrease of <50% or no change in size of measurable disease during therapy. Progression was defined as an increase by ≥25% of the product of perpendicular diameters of tumor lesions or appearance of new metastatic lesions. Time to progression was measured from the first day of therapy. Duration of response was measured from the date of first documentation of response. Survival was measured from the date of entry into study.

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**Table: Treatment Scheme**

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Days 8 through 14 at home.

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**Fig. 1** Treatment scheme.
Table 1  Patient characteristics

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<td>Patients with metastatic disease</td>
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Pharmacology Studies

**5-FU and Uracil Plasma Concentrations.** Serial 5-FU and uracil plasma concentrations were obtained prior to treatment and at 8 a.m. and 5 p.m. on days 3 and 4 of cycles 1 and 3. Blood (10 ml) was collected into EDTA-containing tubes, and the tubes were immediately centrifuged (10 min, 2500 rpm). The supernatant plasma was transferred into 5 ml polypropylene tubes and stored at −80°C until further analysis. Plasma (1.0 ml) containing internal standard (100 ml of 1.0 mm 5-chlorouracil) was extracted using 8 ml of ethyl acetate. After centrifugation, the clear supernatant was transferred to a clean test tube, and the ethyl acetate was evaporated under nitrogen. The dry sample was reconstituted in 230 μl of dH2O. The sample (100 μl) was injected onto four serially connected 10-μm Bondapak C18 columns (3.9 × 300 mm each; Waters, Milford, MA). Components were separated using a mobile phase system consisting of 20% acetic acid, 1% acetonitrile, and 79% dH2O at a flow of 0.9 ml/min for 20 min; 20% acetonitrile and 80% distilled H2O at 1 ml/min from 20 to 25 min; and 20% acetic acid, 1% acetonitrile, and 79% dH2O at a flow of 0.9 ml/min from 25 to 50 min. UV absorbance at 275 nm was determined using an L-4250 variable wavelength detector (Hitachi Ltd., Tokyo, Japan). Under these conditions, 5-FU elutes at 17 min, uracil at 20 min and 5-chlorouracil at 30 min. Both the intraassay coefficient of variation and interassay coefficient of variation are <10% for the entire standard range. Standards ranged from 100 to 1,025 ng/ml for 5-FU and from 1,000 to 14,000 ng/ml for uracil. The extraction efficiency for 5-FU and uracil ranged from 38 to 49% and 65 to 83%, respectively.

**DPD Assay.** Blood (~30 ml) was collected in heparinized tubes between 8 and 10 a.m. prior to treatment and during chemotherapy on two cycles for determination of DPD activity in PBMCs. Lymphocytes were isolated from whole blood using a Ficoll gradient, as described previously (22). Remaining RBCs were lysed with dH2O, and lymphocytes were resuspended in 35 mm phosphate buffer after centrifugation. A crude cytosol was prepared by sonication, and cellular debris was separated by centrifugation at 20,000 × g for 30 min. Cytosol from tumor samples was obtained by homogenization on ice using an OMNI-1000 tissue homogenizer at 30,000 rpm for 60 s.

Table 2  Significant hematological toxicities

<table>
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<th>Thrombocytopenia</th>
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a Cancer and Leukemia Group B Expanded Common Toxicity Criteria.
b Patient died from neutropenic sepsis during cycle 4.
c Patient died during cycle 1. N/A, not applicable.

Varying amounts of cytosolic protein (20–60 μg) were incubated at 37°C in the presence of 2.9 nmol of [14C]5-FU, 31.25 nmol of NADPH, and 312.5 nmol of MgCl2 (total volume of 125 ml). The reaction was stopped after 60 min by addition of ice cold ethanol, and solids were precipitated by centrifugation. After evaporation of the liquid, the solids were reconstituted in a 300-μl high-performance liquid chromatography mobile phase (0.005 m tetraethylammonium hydrogen sulfate and 0.0015 m potassium phosphate). Conversion of 5-FU to dihydro-5-FU was determined by reverse-phase high-performance liquid chromatography using a C18 Bondapak column and the above mobile phase. Flow rate was 1 ml/min, and detection was by radiometric detector. Enzyme activity was calculated as nmol of 5-FU converted/mg protein/min.

**Statistics**

For each patient, the four “on-cycle” measurements were averaged to yield mean 5-FU and uracil concentrations. Variability in the time of drug dosing did not permit consistent relationships between sampling time and drawing of blood samples. Mean values for 5-FU and uracil concentrations were transformed using logarithms. WBC, absolute neutrophil, and platelet nadirs were each regressed separately on mean 5-FU and uracil concentrations for both cycles 1 and 3. Regression of platelet nadirs were each regressed separately on mean 5-FU dose and uracil concentration.

**RESULTS**

Thirteen patients were enrolled on the study between July 1996 and June 1997. Patient characteristics are outlined in Table 1. Nine of the 13 patients had recurrent disease, and 4 had received previous RT (3240–7240 cGy). The first patient enrolled on the protocol received daily RT (200 cGy/dose) for a total of 7 cycles (total dose = 7000 cGy). The remaining 12 patients received twice-daily radiation at 150 cGy/dose.

**Dose Escalation.** Intrapatient dose escalation was permitted. Five patients initiated therapy at dose level 1 (2.5 mg/m²...
5-FU. Of these five patients, four were escalated to dose level 2 (5.0 mg/m² 5-FU) once three patients had completed two cycles at dose level 1 without significant toxicity. The first patient enrolled at dose level 1 actually completed treatment at dose level 3 (7.5 mg/m²). This patient received once daily radiation for a total of seven cycles. The remaining eight patients were enrolled at dose level 2. Two of these patients were escalated to dose level 3. One patient, who had been escalated to dose level 3, died as a result of neutropenic sepsis following cycle 4 of treatment. This same patient also had grade 4 thrombocytopenia. The other patient, who had been escalated to dose level 3, experienced no significant toxicity but was dose-reduced following the on-study death. All subsequent patients were being treated (Fig. 2). Complete or nearly complete inactivation of DPD was achieved in all patients. The one patient with incomplete inactivation of DPD had the lowest serum 5-FU concentrations (average = 58 ng/ml) of all patients treated at dose level 2 (5.0 mg/m² 5-FU). Also of interest, several patients exhibited low DPD activity in their PBMCs at baseline. Specifically, patient 2 had no measurable DPD activity prior to treatment. Traditional dosing of 5-FU might have produced severe toxicity in this patient.

Steady-state plasma 5-FU and uracil concentrations were also monitored by obtaining blood samples in the morning and afternoon on days 4 and 5 of two different treatment cycles (Fig. 2). There was wide interpatient variability in plasma 5-FU concentrations at a given dose level. Likewise, there was substantial intrapatient variability in 5-FU concentrations (data not shown). The intrapatient variability did not correspond to timing of the blood samples. Plasma 5-FU concentrations did, however, increase with increased dose. For those patients beginning therapy at dose level 1 and escalating to dose level two, the mean 5-FU concentration at dose level 1 (2.5 mg/m²) was 54.6 ng/ml, compared to 145.7 ng/ml at dose level 2. For patients receiving all treatments at dose level 2 (5.0 mg/m²), average 5-FU plasma levels were not different between cycles 1 and 3. No samples for plasma 5-FU determinations were obtained at dose level 3 (7.5 mg/m²). Average 5-FU plasma concentrations correlated inversely with absolute neutrophil count nadirs, but no correlation was observed with other toxicities.

Uracil concentrations were monitored as an indirect measurement of DPD inactivation. In all patients, uracil levels were markedly elevated following the administration of eniluracil (Fig. 3C). Baseline uracil levels were below the detection limits of the assay. Although all patients received the same dose of eniluracil, significant variability in plasma uracils was seen. Plasma 5-FU concentrations and uracil concentrations correlated directly.

Responses. Of the 13 patients treated on this protocol, 6 were evaluable for response (Table 4). Two died of toxicities while on treatment. Five patients had undergone surgery prior to therapy.

### Table 3  Significant nonhematological toxicitiesa

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<td>13b</td>
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*a No respiratory toxicities or alopecia seen.
*b Cancer and Leukemia Group B Expanded Common Toxicity Criteria.
*c Patient died from neutropenic sepsis during cycle 4.
*d Patient died during cycle 1. N/A, not applicable.

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treatment with chemoradiotherapy and had no measurable disease. One patient had progressive disease during treatment. Of the remaining five evaluable patients, three had pathologically documented CRs. One patient had a clinical CR in the RT treatment field, but disease progressed in the lung. One patient had a clinical partial response and died 3 months after completing therapy. As of October 1, 1998, 5 of the 13 patients treated on this study were alive: 4 without evidence of disease and 1 with recurrence.

**DISCUSSION**

This Phase I study was undertaken to determine the feasibility of substituting the combination of eniluracil and oral 5-FU for continuous infusion 5-FU in an established radiosensitizing regimen of 5-FU and hydroxyurea. Oral dosing of 5-FU would permit complete oral dosing of chemotherapy, facilitating outpatient treatment and obviating the need for permanent venous access devices.

Previous studies in patients with colon cancer using a 5-day schedule of eniluracil (20 mg BID) and oral 5-FU given every 28 days, reported myelosuppression, specifically neutropenia, as the principal toxicity (23). The recommended Phase II dose of 5-FU using this regimen was 25 mg/m². In this study, the frequency of dosing was increased to every 14 days. Because of the increased dosing frequency, the initial dose levels of 5-FU were quite low. In fact, intrapatient dose escalation was planned due to concerns of inadequate 5-FU dosing at the initial low dose levels. Surprisingly, DLTs, including two patient deaths, were observed at dose levels of 5-FU of ≤7.5 mg/m². As in the previous studies using a 5-day regimen, myelosuppression was the principal DLT. Toxicities were not observed until later in the treatment course, typically cycles 4 and 5. Mucositis and/or dermatitis, which are typically dose-limiting in studies examining radiosensitizing chemotherapy combinations, were not excessive and not significantly greater than would be anticipated with the administration of twice-daily RT alone. Thus, the myelotoxicity of this regimen far outweighs the potential benefit from radiosensitization. The study was discontinued before hydroxyurea was added to the regimen.

In addition to clinical end points, measurement of DPD activity and 5-FU and uracil plasma concentrations were included to document adequate dosing of the drugs in this unique patient population. Adequate dosing of eniluracil was confirmed by the inactivation of DPD in PBMCs, the elevated plasma...
uracil concentrations, and the dose-dependent response of 5-FU plasma concentrations with oral dosing of 5-FU. Average plasma 5-FU concentrations achieved at the 5.0 mg/m² BID dose level were comparable, although slightly lower than those published previously for continuous infusion 5-FU at 640 mg/m² in the FHX regimen (24). The absence of radiosensitization can be attributed to our inability to add hydroxyurea to the regimen. Hydroxyurea potentiates the radiosensitizing effects of 5-FU, and the combination is responsible for the significant clinical radiosensitization seen with the FHX regimen. 5-FU concentrations did correlate inversely with neutrophil counts, although too few data were obtained to draw significant conclusions regarding specific mechanisms responsible for this surprising myelotoxicity.

Explanations for the excessive myelotoxicity are not readily apparent. The increased frequency of dosing of the eniluracil and 5-FU combination certainly contributed to the level of toxicity seen at such low doses of 5-FU. However, the toxicity is clearly not exclusively an effect of 5-FU dosing, considering higher 5-FU plasma concentrations are routinely achieved using infusional 5-FU given 5 days every other week in our other chemoradiotherapy protocols. Other explanations include an enhancement of 5-FU activity in myeloid precursors resulting from local DPD inactivation or perhaps effects of elevated plasma uracil concentrations.

In conclusion, cumulative myelosuppression, both neutropenia and thrombocytopenia, is the significant DLT of oral 5-FU and eniluracil given with RT in this every-other-week dosing scheme. No significant radiosensitization was observed at the tolerated dose levels. Alternative dosing schedules need to be examined to determine the most appropriate use of the combination of 5-FU and eniluracil with RT. A continuous 28-day dosing schedule of eniluracil and 5-FU is currently being studied in patients with colorectal cancer. Myelosuppression has not been limiting according to preliminary reports. A similar continuous dosing schedule, combined with continuous daily RT, is being considered.

REFERENCES


Phase I Study of Eniluracil, a Dihydropyrimidine Dehydrogenase Inactivator, and Oral 5-Fluorouracil with Radiation Therapy in Patients with Recurrent or Advanced Head and Neck Cancer


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