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Clinical report

Peripheral neuropathy associated with weekly oral 5-fluorouracil, leucovorin and eniluracil

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5-Fluorouracil (5-FU)-associated neurotoxicity is uncommon; symptoms may occur abruptly or more gradually during the course of chemotherapy. Peripheral neuropathy with 5-FU therapy has only rarely been reported. Two patients treated in a phase I trial of oral 5-FU, leucovorin and eniluracil, an inhibitor of dihydropyrimidine dehydrogenase (DPD), developed delayed onset symptoms of unsteady gait and reduced sensation in the legs. Magnetic resonance imaging scans of the brain and neurologic examination did not support a CNS basis for the condition. Electromyograms and nerve conduction studies revealed sensorimotor polyneuropathy. Other common etiologies of peripheral neuropathy were excluded. The neurological condition of these patients stabilized after 5-FU dose reduction and partial resolution gradually occurred when protocol therapy was stopped. Although CNS symptoms may rarely complicate 5-FU therapy, peripheral neuropathy is unexpected. Patients with DPD deficiency treated with conventional doses of 5-FU typically develop acute CNS toxicity shortly after therapy, accompanied by extremely high systemic exposure to 5-FU. Patients with normal 5-FU clearance may also experience CNS toxicity, particularly with high-dose schedules, and both parent drug and its catabolites may be contributory. Since DPD was profoundly inhibited during eniluracil therapy in these two patients, it is likely that 5-FU or its active metabolites were contributing factors to the peripheral neuropathy. [© 2001 Lippincott Williams & Wilkins.]

Key words: Dihydropyrimidine dehydrogenase, eniluracil, fluorouracil, peripheral neuropathy.

Introduction

The pyrimidine antimetabolite 5-fluorouracil (5-FU) was first used clinically as an anti-cancer agent over 40 years ago and is now commonly employed as a component of therapy for a variety of epithelial malignancies. The spectrum of toxicity differs according to the schedule of administration, and the most common side effects include stomatitis, diarrhea, myelosuppression and cutaneous toxicity.[1] Neurotoxicity is a less frequent side effect, but the most commonly described CNS toxicity is a cerebellar syndrome characterized by ataxia, which may be accompanied by global motor weakness, bulbar palsy, bilateral oculomotor nerve palsy and upper motor neuron signs.[1–3] Serious cognitive impairment such as difficulty concentrating, somnolence, coma and organic brain syndrome or dementia have also been seen.[1,4,5] These symptoms are usually reversible upon discontinuation of the drug. Neurologic toxicity has been reported most often with schedules that employ high intermittent doses of 5-FU given by either bolus injection or as an infusion over 24–48 h, and with intensive daily schedules.

Administration of 5-FU as a weekly high-dose 24 h infusion alone or with leucovorin (LV) modulation is an active schedule with a favorable toxicity profile in terms of mucositis, diarrhea and myelosuppression. However, cerebellar toxicity can be dose limiting.[6,7] We conducted a phase I trial involving oral eniluracil, 5-FU and LV intended to simulate a weekly high-dose 24-h infusion of 5-FU. By potently inhibiting dihydropyrimidine dehydrogenase (DPD), eniluracil prevents the formation of potentially neurotoxic metabolites of 5-FU.[8] We anticipated that CNS toxicity would not occur this regimen. During the conduct of this trial, two patients developed delayed onset symptoms of unsteady gait. The initial assumption was that these symptoms represented the well-described cerebellar ataxia. While no CNS abnormalities were evident, both patients had neurologic

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evidence of peripheral neuropathy as the causal factor.

Peripheral neuropathy has been reported with 5-FU given in combination with chemotherapy agents that are known to produce cumulative peripheral neuropathy such as platinum analogs and taxanes. To our knowledge, there has been only one prior report describing two patients who developed a delayed onset peripheral neuropathy following administration of 5-FU.[9] Herein we describe the clinical and neurophysiological findings of two additional patients who developed peripheral neuropathy during 5-FU-based therapy and discuss the potential implications of this unusual toxicity in relation to the more commonly described 5-FU-associated CNS toxicities.

Patients and methods

Study protocol

The major objective of this dose-escalation trial was to determine the recommended dose of oral 5-FU given in combination with fixed doses of eniluracil and LV on a weekly schedule. Standard eligibility criteria for a phase I trial applied. To serve as a reference for the pharmacokinetic studies, patients received an initial cycle of 5-FU 2300 mg/m^2 given as a 24-h continuous i.v. infusion on day 2, with low-dose oral LV given on days 1, 2 and 3. Two weeks later, the patients began therapy with oral eniluracil and LV days 1–3, with oral 5-FU given on day 2; the regimen was repeated weekly for 3 of 4 weeks. The initial schedule involved twice daily administration of the study drugs and the results of 12 patients who received this initial schedule have been published.[10] The pharmacologic and pharmacodynamic results in the initial cohort of 12 patients led us to amend the protocol to evaluated single daily dosing of oral eniluracil 20 mg and LV 30 mg days 1–3, with 5-FU given in escalating doses starting with 15 mg/m^2 p.o. day 2. The Cancer Therapy Evaluation Program, National Cancer Institute, and the Institutional Review Boards of the National Cancer Institute and the National Naval Medical Center approved the clinical protocol, and all patients signed informed consent.

Patients

Sixteen patients (eight males and eight females) were enrolled on the amended schedule between October 1998 and October 1999. The median age was 61.5 years (range 32–72) and the median Eastern Cooperative Oncology Group performance status was 1 (range 0–2). The histologies included colon, 10; pancreas, 2; and cholangiocarcinoma, rectal, leiomyosarcoma and cervical, 1 patient each. The median number of cycles received by these patients was 2.5 (range 1–12).

Measurement of DPD activity

DPD activity was measured by an *ex vivo* radioisotopic assay using lysates of peripheral blood mononuclear cells as previously described.[10]

Table 1. Summary of patients who developed peripheral neuropathy following administration of 5-FU-based chemotherapy

Reference	Age/ gender	5-FU (mg/m^2)	Concurrent chemotherapy	Neurotoxicity	Treatment	Outcome
Stein *et al.*[9]	71 male	450 i.v. push daily × 5	levamisole	pain in lower limbs	Rx discontinued	neurotoxicity stabilized until patient re-challenged with 5-FU and LV for liver metastasis; subsequent deterioration required discontinuation of 5-FU/LV
Stein *et al.*[9]	54 female	450 i.v. push daily × 5	levamisole	pain and numbness in lower limbs	Rx discontinued	improved but incomplete resolution
Current report	65 male	65 p.o. days 1–3 weekly × 3 of 4 weeks	leucovorin plus eniluracil	reduced sensation in leg leading to unsteady gait	5-FU dose reduced	symptoms stabilized with dose reduction; gradually improved after therapy stopped with persistent foot drop
Current report	70 male	23 p.o. days 1–3 weekly × 3 of 4 weeks	leucovorin plus eniluracil	reduced sensation in leg leading to unsteady gait	5-FU dose reduced	symptoms stabilized with dose reduction; gradual but incomplete improvement after Rx stopped

Results

Description of the two patients

The first patient was a 66-year-old male with metastatic colon cancer and a past history of mild hypertension who was not taking any medications. He was a distant ex-smoker with occasional alcohol intake. He was diagnosed with adenocarcinoma of the splenic flexure in 1992 and underwent left hemicolectomy for stage III carcinoma. The patient declined adjuvant chemotherapy. In 1994, a rise in the carcinoembryonic antigen (CEA) prompted computerized tomographic (CT) imaging which revealed a single liver metastasis. Resection of the liver metastasis was performed, followed by chemotherapy with 6 months of weekly 5-FU and LV. In 1998, a CEA rise led to discovery of biopsy-proven metastatic pulmonary adenocarcinoma. He entered our protocol of oral 5-FU, LV and eniluracil. He experienced no toxicity with the initial reference treatment of oral LV 30 mg p.o. days 1–3 and 5-FU 2300 mg/m^2/24 h. Two weeks later, he began the oral regimen with a starting 5-FU dose of 15 mg/m^2. He tolerated the therapy extremely well and received four dose escalations up to 63 mg/m^2 by cycle 7. A partial response to therapy was confirmed after six cycles. After receiving the first week of therapy during the seventh cycle, he experienced non-neutropenic fever, symptoms of upper respiratory infection and unsteady gait. The cycle was stopped and he was treated with oral antibiotics. When he returned to clinic 2 weeks later, he reported persistent unsteady gait that was of grade 2 severity (affecting some specialized activities, but not interfering with his ability to carry out activities of daily living). While no abnormal CNS findings were evident on physical examination, impaired heel–toe walking, diminished sensation to pinprick in the lower extremities and decreased distal motor strength were noted. Because of his excellent response to chemotherapy, he continued on protocol with a 25% reduction in the 5-FU dose to 51 mg/m^2. Upon evaluation for his 10th cycle of therapy, persistent unsteady gait prompted a delay in therapy until a more detailed neurologic evaluation could be performed. A magnetic resonance imaging (MRI) scan of the brain was unremarkable, as were the routine laboratory studies. Diagnostic work-up for other etiologies of peripheral neuropathy indicated that vitamin B_{12}, TSH, rheumatoid factor and thiamine levels were normal, and antibodies against double-stranded DNA phospholipid and cardiolipin were negative. The patient was not receiving any other potentially neurotoxic medications. Nerve conduction studies and electromyogram revealed acute, axonal sensorimotor polyneuropathy with secondary demyelinative features, with an increasing proximal to distal neuropathic gradient. A diagnostic sural nerve biopsy was considered, but the patient declined. The symptoms slightly improved with a 3-week treatment delay from the planned start of the cycle. After extensive discussion, the decision was to continue protocol therapy with a further 25% dose reduction to 34 mg/m^2 and careful follow-up of his neurologic status. He had three more cycles with no clinical change in neurological signs or symptoms. Protocol therapy was discontinued after 12 cycles due to progression of pulmonary metastases; the total cumulative oral doses of 5-FU and eniluracil were 1340 mg/m^2 (2790 mg) and 2040 mg, respectively. Six weeks later, he began irinotecan on a weekly for 4 of 6 weeks schedule. The patient had gradual improvement in his gait, balance and coordination. Physical exam 7 months after discontinuing eniluracil/5-FU/LV revealed residual grade 2 sensory loss in the feet and grade 1 motor loss with dorsiflexion.

The second patient was a 69-year-old man with metastatic colon cancer who had been in good general health on no medications. In 1996, a routine fecal occult blood testing was positive. Subsequent colonoscopy revealed a sigmoid adenocarcinoma and he underwent sigmoid colectomy. He received 1 year of adjuvant chemotherapy with 5-FU and levamisole for stage II disease, which was well tolerated. Eighteen months later, a rise in the CEA was noted. CT scans of the chest and abdomen and MRI scan of the abdomen were negative. Exploratory laparotomy revealed enlarged lesser curve gastric nodes which were biopsy-positive for metastatic adenocarcinoma. He was referred for enrollment onto the oral 5-FU/LV/eniluracil protocol. The single treatment of oral LV 30 mg p.o. days 1–3 and 5-FU 2300 mg/m^2/24 h was well tolerated. Two weeks later, he began the oral regimen with a starting 5-FU dose of 15 mg/m^2. Both of the patients were documented to have profound inactivation of DPD activity during eniluracil therapy (Figure 1). Because this patient experienced minimal toxicity, he received two 25% dose escalations up to 23 mg/m^2 5-FU by cycle 5. During the seventh cycle, he complained of unsteadiness when walking, especially when he initially stood up; this toxicity was judged to be grade 2 in severity. Restaging CT scans showed no evidence of disease progression and the patient wished to remain on study at a reduced 5-FU dose (19 mg/m^2); a detailed neurologic evaluation was planned. Physical examination showed no evidence of CNS abnormalities; motor strength was grossly normal throughout, but decreased pinprick, light touch and proprioception were noted in the right and left lower extremities along with impaired heel–toe walking. MRI

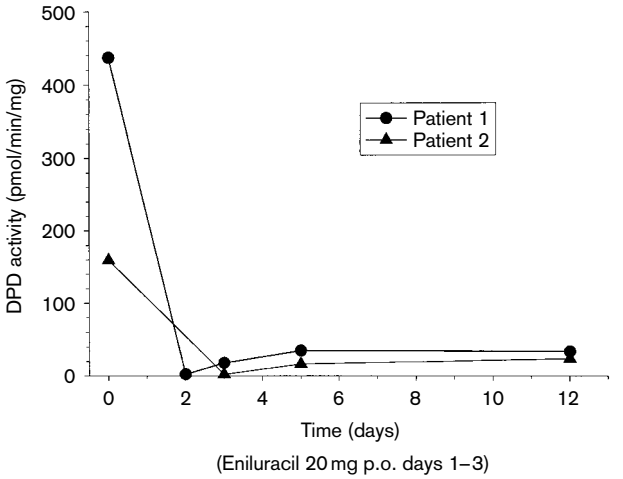

Figure 1. DPD activity in the two index cases during therapy with oral 5-FU/LV and eniluracil. Profound inactivation of DPD activity was evident during and up to 2 weeks after eniluracil therapy.

scan of the brain showed a mild degree of small vessel ischemic changes in the white matter, but no evidence of metastasis, mass effect or cerebellar abnormalities. Nerve conduction studies revealed evidence of polyneuropathy and the pattern was consistent with a sensory/motor axonal neuropathy. Laboratory data including electrolytes, vitamin B_{12}, TSH and studies for autoimmune diseases did not reveal any abnormalities. The patient received three additional complete cycles at 19 mg/m^2 with no worsening of his symptoms before protocol therapy was discontinued for disease progression. The total cumulative doses of 5-FU and eniluracil were 642 mg/m^2 (1610 mg) and 1980 mg, respectively. Repeat EMG and nerve conduction studies at that time were stable with mixed axonal and demyelinating sensorimotor polyneuropathy. He subsequently received irinotecan for two cycles with marked toxicity (diarrhea and fatigue) despite dose reductions. A CT scan showed stable disease, but in view of the treatment-associated toxicity, this treatment was discontinued. Clinical evaluation 2 months later indicated no subjective improvement, although there appeared to be improvement in the sensory loss in his lower extremities.

Discussion

Neurological side effects associated with bolus administration of 5-FU were first reported in 1964.[2,3] Symptoms of cerebellar ataxia developed after a median of 10 weekly treatments and complete neurological recovery occurred within 2–4 weeks after stopping 5-FU. Since these initial reports, CNS toxicity has been reported by other investigators with a variety of 5-FU schedules. CNS toxicity is rarely dose limiting, but the incidence and severity are clearly influenced by the dose and schedule of 5-FU, and concurrent use of other chemotherapy agents. Acute encephalopathy may be manifest by insomnia, difficulty concentrating, confusion, stupor or coma. Cerebellar findings may range from simple gait ataxia to a more florid pan-cerebellar syndrome accompanied by global motor weakness, bulbar palsy, bilateral oculomotor nerve palsy and upper motor neuron signs. These symptoms are usually reversible upon discontinuation of 5-FU.

Modulators such as thymidine, *N*-(phosphonacetyl)-L-aspartic acid (PALA), LV, allopurinol and interferon may accentuate 5-FU-associated neurotoxicity.[1,11–13] In general, these modulatory agents are intended to either enhance the formation of the active metabolites of 5-FU or potentiate its cytotoxic effects. Whether patients with pre-existing medical conditions associated with neuropathy are at increased risk for developing symptomatic neurotoxicity with 5-FU therapy is unclear.

Other antimetabolites including methotrexate, cytarabine and fludarabine have been associated with chronic encephalopathy or 'subcortical dementia' occurring months to years after treatment, particularly when these agents are combined with cranial radiation. Intravenous 5-FU given alone or with LV modulation has not been associated with this form chronic encephalopathy. However, a cerebral demyelinating process reminiscent of multifocal leukoencephalopathy has been reported as an uncommon complication of therapy with 5-FU and levamisole, an anti-helminthic drug and putative immunomodulator.[14,15] The symptoms in these patients occurred after several months of adjuvant therapy with 5-FU/levamisole, and included a decline in mental status, ataxia and loss of consciousness. MRI scans with gadolinium enhancement showed prominent multifocal enhancing white matter lesions. Cerebral biopsy performed in two patients showed morphological features of an active, demyelinating disease. The myelin loss was associated with both dispersed and vasocentric macrophage infiltration, sparing of axons, and peri-vascular lymphocytic inflammation. Several patients improved after cessation of therapy and a short course of corticosteroids, while recovery was incomplete in other patients.

5-FU crosses the blood–brain barrier and attains considerable concentrations within the cerebrospinal fluid. The biochemical basis for neurological toxicity associated with 5-FU is incompletely understood, but

is likely to be multi-factorial. *In vivo*, 5-FU is readily converted to dihydrofluorouracil by DPD; a subsequent enzymatic step produces fluoreidopropionic acid; finally, β-alanine synthase mediates the formation of fluoro-β-alanine (FBAL) with the release of carbon dioxide and ammonia.[1] FBAL has a much slower clearance and a longer half-life compared to 5-FU. Acute CNS toxicity has been described in both DPD-deficient and -proficient patients.[16–19] Anecdotal reports suggest that thiamine administration may ameliorate acute Wernicke–Korsakoff-like encephalopathy,[5,20] and in one DPD-deficient patient, a continuous i.v. infusion of thymidine was associated with recovery from 5-FU-associated coma.[19]

Preclinical models suggest a possible role for 5-FU catabolites.[21–25] Exposure of cerebellar cultures established from brains of 1-day-old mice to concentrations of either 7 or 70 μM FBAL or fluoroacetate was associated with apparent selective concentration- and time-dependent injury to myelin, with sparing of the oligodendrocytes and neurons.[21] In contrast, exposure to 7 μM of either β-alanine and acetic acid (the two physiological counterparts) or to 5-FU did not produce injury to myelin fibers. Following systemic administration of radiolabeled FBAL to rats, prolonged accumulation of [^{3}H]FBAL occurs in brain tissues.[26] In a canine model, neurotoxicity is dose limiting with a 72 h infusion of 5-FU, but systemic administration of eniluracil abrogates the neurotoxicity.[8] In a feline model, administration of either oral 5-FU or direct instillation of FBAL into the left ventricle produced similar neuropathologic abnormalities.[23,24] Intraventricular administration of 10 mg 5-FU to rhesus monkeys is not associated with clinical signs of neurotoxicity, even though the peak ventricular concentrations exceed 10 mM and the elimination half-life is almost 1 h.[27] In contrast, intralumbar administration of the same 5-FU dose led to delayed onset of bilateral hind limb paralysis. Histopathologic changes at necropsy ranged from demyelination of the lumbar and sacral cords to severe necrosis of the ventral horn of the sacral spinal cord.[27] Of note, other investigators have reported that the deoxyribonucleoside metabolite of 5-FU, fluorodeoxyuridine, can be safely administered to rats by the intrathecal route.[28] Since the activity of thymidine phosphorylase, which is capable of converting fluorodeoxyuridine to 5-FU, is negligible in cerebrospinal fluid, high local concentrations of 5-FU appear to be implicated in the demyelination seen in this primate model.

While peripheral neuropathy has been reported as a common complication of systemic therapy of 5-FU given in combination with platinum analogs and taxanes, the incidence and severity of peripheral neuropathy seems to be in accordance with that anticipated with the use of platinum analogs or taxanes alone. Stein and colleagues[9] reported two patients who developed peripheral neuropathy in association with 5-FU-based therapy. Both patients received postoperative pelvic radiation with radiosensitizing doses of i.v. bolus 5-FU 375 mg/m^2 i.v. the first and last 3 days of radiation for either locally invasive adenocarcinoma of the sigmoid colon with bladder involvement, or for rectal cancer. Six weeks later, adjuvant chemotherapy with 5-FU 450 mg/m^2 i.v. plus levamisole 150 mg p.o. in three divided doses daily for 5 consecutive days each month was initiated. During chemotherapy, the first patient developed pain in the lower legs, with weakness on dorsiflexion, decreased pinprick sensation and decreased vibration sensation. Neurophysiologic studies were consistent with a demyelinating polyneuropathy mainly involving large fibers. The adjuvant therapy was discontinued, with stabilization of symptoms and signs on both physical exam and NCS. Three months later, the patient developed liver metastases and he received a daily for 5 days schedule 5-FU/LV (425/20 mg/m^2/day). After one course, the patient had symptomatic neurologic deterioration, which was confirmed by physical exam and neurophysiologic studies, necessitating discontinuation of 5-FU-based therapy. The second patient complained of pain and numbness in the lower extremities after completion of 6 monthly cycles of 5-FU/levamisole. Neurologic exam revealed absent distal abnormalities in deep tendon reflexes, decreased pinprick and vibration sensation, and unsteady gait. Neurophysiological studies revealed large-fiber demyelinating polyneuropathy. The symptoms gradually improved off therapy, but abnormalities persisted on neurological exam.

Our patients were not receiving levamisole, but rather an oral regimen of 5-FU modulated by LV and eniluracil. The results of several clinical studies involving oral administration of 5-FU and eniluracil have been published. The most common schedule involves chronic daily administration of 5-FU at doses ranging from 1 to 1.35 mg/m^2 and eniluracil at approximately a 10-fold higher dose twice daily for 28 of 35 days.[29,30] One of 36 patients treated on a phase I trial with this chronic schedule developed delayed neurologic toxicity.[29] The patient had renal carcinoma, and had previously received both paclitaxel and cisplatin-based therapy. The patient had pre-existing sensory neuropathy involving the soles of his feet when he began protocol therapy. After 1 year of therapy with eniluracil/5-FU, he complained of erectile dysfunction and 3 months later developed difficulty walking with unsteady gait. MRI scan

revealed cerebellar atrophy, particularly in the cerebellar vermis. Protocol therapy was discontinued, and the impotence and gait disturbance improved over the next three months. Mani *et al*. reported the results of a phase II study of the 28-day regimen of oral 5-FU/eniluracil in 55 patients with metastatic colon cancer.[30] Three patients were described with neuromotor and sensory toxicity that was possibly treatment related. One patient developed reversible grade 2 ataxia. Another patient who first experienced weakness and unsteady gait during the initial cycle developed worsening weakness, ataxia and nystagmus during cycle 2. CT and MRI scans of the brain revealed white matter changes consistent with small vessel ischemia, while CSF examination was unremarkable. Persistent nystagmus was noted following discontinuation of therapy. A third patient with long-standing diabetes developed partially reversible grade 2 sensorimotor weakness in the lower extremities during therapy. Of these three cases, only the signs and symptoms of the latter patient are suggestive of peripheral neuropathy.

In summary, we describe two patients with no known pre-disposing factors who developed signs and symptoms of peripheral sensorimotor neuropathy while receiving investigational therapy with oral 5-FU/LV and eniluracil intended to mimic a weekly high-dose 5-FU infusion schedule. Cerebellar toxicity is an expected side effect with the weekly schedule of high-dose 5-FU over 24 h. No evidence of acute or delayed CNS toxicity has been observed in 12 patients treated with the initial twice daily schedule or in the 16 patients treated with the once daily schedule on this protocol. Peripheral neuropathy was not expected. Although we did not have pre-treatment neurophysiological studies in the two patients reported herein, neither had symptoms of peripheral neuropathy at study entry and neurologic exam done as part of the pre-therapy physical exam was unremarkable. Following the onset of symptoms in these two index cases, the protocol was amended to include the risk of peripheral neuropathy in the consent form; further, baseline and serial neurologic evaluation were planned, and blood studies to rule out other common causes of peripheral neuropathy were included. However, no other patients have experienced signs or symptoms of peripheral neuropathy. Since we documented profound inhibition of DPD activity in these two patients, it is highly unlikely that 5-FU catabolites were a contributing factor. Rather, either parent drug, or more likely an active metabolite, may be responsible. The contribution of LV is unclear, but in general this is used to enhance 5-FU-associated thymidylate synthase inhibition. Chronic administration of single-agent eniluracil has not been explored in the preclinical setting, but short-term studies in animals and humans suggest no acute toxicity. Although symptoms of unsteady gait complicating 5-FU therapy are usually attributed to cerebellar toxicity, peripheral neuropathy may also produce similar symptoms. A careful neurologic exam will distinguish between these two entities, but in either case, 5-FU dose reduction or discontinuation is indicated.

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