Peripheral neuropathy exacerbation associated with topical 5-fluorouracil

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Peripheral neuropathy secondary to 5-flourouracil and capecitabine (Xeloda) has been reported. We report the first case of exacerbation of peripheral neuropathy related to topical 5-flourouracil (Efudex). A 70-year-old Caucasian male with a history of actinic keratosis for 15 years was treated intermittently with topical application of 5-flourouracil. He also developed sensory peripheral neuropathy around the same time, but extensive work-up disclosed no clear etiology. In early 2005, he developed an exacerbation of his peripheral neuropathy following a 21-day course of topical 5-flourouracil for actinic keratosis, especially pain and parasthesias. Dihydropyrimidine dehydrogenase activity was evaluated in the peripheral mononuclear cells both by radioassay and by [2-^{13}C] uracil breath test. Dihydropyrimidine dehydrogenase activity was within the normal range by both methods. Stopping topical 5-flourouracil resolved the symptoms to baseline. Instead of topical 5-flourouracil, topical imiquimod was used which did not exacerbate his neuropathy. He was not re-challenged with topical 5-flourouracil. Topical 5-flourouracil has been known to cause mainly dermatological adverse effects, but systemic effects because of absorption are possible, especially in dihydropyrimidine dehydrogenase-deficient patients. As our patient had no other cause responsible for his neuropathy, the onset of symptoms coincided historically with topical application of 5-flourouracil and the 5-flourouracil usage preceded an exacerbation of sensory symptoms, we conclude that this drug was responsible for his polyneuropathy. *Anti-Cancer Drugs* 17:1095–1098

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Introduction

5-Fluorouracil (5-FU), first introduced as a rationally synthesized anticancer agent 30 years ago, continues to be widely used in the management of several common malignancies, including cancer of the colon, breast and skin [1]. This drug, an analog of the naturally occurring pyrimidine uracil, is metabolized via the same metabolic pathways as uracil [1]. It is used as an intravenous infusion, orally and as a topical agent. Common systemic toxicities normally associated with parenteral administration include neutropenia and gastrointestinal toxicity [1,2]. A serious adverse effect, erythrodysesthesia, has also been reported [3]. Severe cardiotoxicity and infarction has also been documented [4]. Toxicity of 5-FU generally depends upon route and duration of infusion. Neurological side-effects associated with systemic administration of 5-FU are of two types: central and peripheral. Central neuropathy can manifest as cerebellar syndrome characterized by ataxia, which may be accompanied by global motor weakness, bulbar palsy, bilateral oculomotor nerve palsy and upper motor neuron signs, or an acute encephalopathy manifesting as insomnia, difficulty in concentrating, confusion, stupor or coma [4–7]. On the other hand, peripheral neuropathy has been reported rarely in patients receiving therapy of 5-FU with biomodulators or when given in combination with platinum analogs and taxanes [8]. We have previously reported on patients who developed peripheral neuropathy while receiving oral 5-FU with eniluracil [9] as well as capecitabine, an oral pro-drug of 5-FU [10].

Systemic toxicity normally associated with parenteral administration (including neutropenia, neurotoxicity and gastrointestinal toxicity) has been associated with topical use, particularly in patients with a genetic deficiency of dihydropyrimidine dehydrogenase (DPD) [11]. Women, in general, are particularly prone to DPD deficiency [12]. Daily application of 5% strength is associated with minimal systemic absorption and is better tolerated than higher-strength preparations [13]. The most frequent known adverse reactions to topical 5-FU occur locally and are often related to an extension of the pharmacological activity of the drug. These include burning, crusting, allergic contact dermatitis, erosions, erythema,

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hyperpigmentation, irritation, pain, photosensitivity, pruritus, scarring, rash, soreness and ulceration. The most commonly used topical agent is Efudex manufactured by Valeant Pharmaceuticals International (Costa Mesa, California, USA). Efudex cream contains 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate and parabens.

Although most of the topical drug is not absorbed, systemic toxicity to topical 5-FU is a documented phenomenon, especially in persons suffering from DPD deficiency. To our knowledge, there has been no prior report of peripheral neuropathy following application of topical 5-FU. Herein, we describe the clinical and neurophysiological findings of one patient who developed polyneuropathy associated with topical 5-FU (Efudex) for his actinic keratosis and discuss the potential implications of this unusual toxicity in relation to 5-FU. DPD activity was also evaluated in this patient.

Patients and methods

Case report

A 70-year-old Caucasian male was referred to us with an exacerbation of his symptoms of polyneuropathy following a 21-day course of topical 5-FU (Efudex) for actinic keratosis in early 2005. The onset of symptoms was 15 years prior to the recent exacerbation. He was not suffering from any other chronic diseases at that time with the exception of actinic keratosis for which he applied topical 5-FU cream. He had a history of moderate drinking and 30-pack year of smoking cigarettes, which he quit 17 years ago. The neuropathy began initially with parasthesias manifested by numbness and burning sensation of the planter surfaces of the toes and forefeet, attributed initially to the roughness of the shoes. Over the next 5 years, the symptoms became profound, associated with extensive numbness and dysesthesia extending to the heels. Occasionally, he would also experience tinnitus and palpitations.

An evaluation by a neurologist at that time, that included an electromyogram and nerve conduction velocity study, revealed decreased sensation to light touch and vibratory sense, with decreased sural nerve conduction velocity bilaterally. Comprehensive cardiology and otolaryngology work-up failed to reveal any significant pathology. Limiting alcohol intake was strongly recommended by the neurologist. The patient took that advice, which resulted in some improvement of his neurological symptoms as well as his tinnitus and palpitations.

Over the next few years, he was also found to have reflux esophagitis, insomnia and dyslipidemia. His medications included trazodone, atorvastatin, esomeprazole and topical 5-FU for actinic keratosis (one course every 1–3 years). Gabapentin had been tried at 300 mg every night with partial symptomatic relief only.

A neuropathy specialist evaluation after 4 years, in 2002, revealed axonal sensory polyneuropathy–decreased reflexes in lower extremities, decreased vibration, and mildly decreased temperature and light touch sensations distally below the ankles. Comprehensive work-up for neuropathy, including serum thyroid-stimulating hormone, serum B12 level, serum protein electrophoresis, venereal disease research laboratory and erythrocyte sedimentation rate was negative. As no specific cause was found to be responsible for neuropathy, the symptoms were attributed possibly to alcohol intake or genetic susceptibility.

Early last year, the patient reduced alcohol intake markedly with further alleviation of his symptoms. Currently, he takes approximately 4 oz wine with meals. Occasional resumption of moderate drinking, approximately 8 oz of wine, reproduces his sensory symptoms, especially pain. Similar exacerbations are experienced with severe weather changes and application of tanning solutions (containing dihydroxyacetone). When he repeated a course of topical 5-FU last year, his symptoms returned, especially pain and parasthesia.

Due to the suspicion that topical 5-FU may have played a role in the exacerbations of his neurological symptoms, his dermatologist treated him with topical imiquimod instead of topical 5-FU without exacerbation. He has not been re-challenged with topical 5-FU. Later on, DPD activity was also evaluated.

Assessment of dihydropyrimidine dehydrogenase by phenotypic methods

Due to the severe exacerbation of neurological toxicities experienced by the patient when receiving topical 5-FU, we utilized two phenotypic methods to assess the patient's DPD activity.

Peripheral blood mononuclear dihydropyrimidine dehydrogenase radioassay

The procedures used to isolate peripheral blood mononuclear cells (PBMCs) and measure PBMC DPD activity are described in greater detail elsewhere [14]. Sixty milliliters of whole blood were collected into heparanized (green-top) vacutainers at approximately noon. PBMCs were isolated from whole blood using a Ficoll gradient. Isolated PBMCs were washed three times with phosphate-buffered saline and lysed by sonication in an ice bath. Cellular debris was removed from the cytosol by centrifugation. The protein concentration of the cytosol was quantified by a Bradford assay [15]. Two hundred and fifty micrograms of cytosolic protein was added to a reaction mixture containing nicotinamide adenine dinucleotide

phosphate (reduced form), buffer A and [6-^{14}C]5-FU. This reaction mixture was incubated for 30 min. Every 5 min, 130-µl aliquots were removed from the reaction mixture and added to an equal volume of ice-cold ethanol to terminate the reaction. The aliquots were then incubated overnight at −80°C, thawed and filtered to remove protein before high-pressure liquid chromatography analysis. Reversed-phased high-pressure liquid chromatography was used to separate and quantify [6-^{14}C]5-FU and [6-^{14}C]5-FUH$_2$. The amount of [6-^{14}C]5-FUH$_2$ formed at each time point (*y*-axis) was plotted against time (*x*-axis). The rate of [6-^{14}C]5-FUH$_2$ formation was determined from the slope of the line following linear regression analysis. DPD enzyme activity was calculated by dividing the formation rate of [6-^{14}C]5-FUH$_2$ by the amount of protein used in the reaction mixture (i.e. nmol/min/mg protein). On the basis of previous population studies by our laboratory, individuals were considered to have PBMC DPD enzyme activity in the normal range when their fresh PBMC DPD activity was above 0.182 nmol/min/mg protein [15–17]. Alternatively, individuals were considered DPD deficient when their fresh PBMC DPD activity was below 0.182 nmol/min/mg protein [15–17].

[2-^{13}C] Uracil breath test

The procedure of the uracil breath test (UraBT) is described in greater detail elsewhere [18]. To minimize variability resulting from a reported circadian variation in DPD enzyme activity [19], the patient started the UraBT protocol at 8:00 a.m. following an overnight fast. The patient was weighed and a 6-mg/kg aqueous solution of [2-^{13}C] uracil (Cambridge Isotope Laboratories, Andover, Massachusetts, USA) was formulated. The patient donated three baseline breath samples into 1.2 l breath bags (Otsuka Pharmaceuticals, Tokushima, Japan). The aqueous [2-^{13}C] uracil solution was then orally administered. Twenty-one postdose breath samples were collected into 100- ml breath bags (Otsuka Pharmaceuticals) during the 180-min period following [2-^{13}C] uracil administration; postdose breath samples were collected every 5 min for 30 min and every 10 min thereafter. Infrared spectrophotometry (UBiT-IR$_{300}$; Meretek Diagnostics, Lafayette, Colorado, USA) was used to quantify the concentration of $^{13}CO_2$ in the postdose breath samples. The $^{13}CO_2$ concentrations of postdose breath samples were reported in delta over baseline (DOB) notation. The patient's breath profile was constructed by graphing the concentration of $^{13}CO_2$ in breath vs. time (*y*- and *x*-axis, respectively). On the basis of a previous study, individuals were considered to have DPD activity in the normal range when the UraBT DOB$_{50}$ (concentration of $^{13}CO_2$ in breath 50 min after [2-^{13}C] uracil ingestion) was above 128.9 DOB (L5). Alternatively, the individuals were considered to be DPD deficient when UraBT DOB$_{50}$ values were below 128.9 DOB [18].

Results

Quantification of peripheral blood mononuclear cell dihydropyrimidine dehydrogenase radioassay

The patient demonstrated PBMC DPD activity within the normal range; the fresh PBMC DPD activity of the patient was 0.33 nmol/min/mg protein.

Evaluation by uracil breath test

The patient demonstrated a UraBT DOB$_{50}$ within the normal range; the UraBT DOB$_{50}$ was 155.3 DOB.

Discussion

Polyneuropathy refers to a generalized, relatively homogeneous process affecting many peripheral nerves, with the distal nerves usually affected most prominently. It is typically manifested by symmetric distal sensory loss, burning or weakness. It often occurs as a side-effect of medication or as a manifestation of systemic disease. Many types of peripheral neuropathy exist, and the common clinical types include idiopathic, prediabetic/diabetic, hereditary, toxic, inflammatory, systemic/metabolic and compression neuropathies.

Topical 5-FU is recommended for the topical treatment of multiple actinic or solar keratoses, Bowen's disease and a few ophthalmologic conditions. In the 5% strength, it is also useful in the treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. The most frequent known adverse reactions to Efudex occur locally and are often related to an extension of the pharmacological activity of the drug. These include burning, crusting, allergic contact dermatitis, erosions, erythema, hyperpigmentation, irritation, pain, photosensitivity, pruritus, scarring, rash, soreness and ulceration [20]. Systemic toxicity consisting of neutropenia, neurotoxicity and gastrointestinal toxicity normally associated with parenteral administration has been associated with topical use, particularly in patients with a genetic deficiency of DPD [11]. Our patient was, however, had a normal range of DPD activity, underlying the fact that systemic toxicity can also manifest in DPD-proficient patients following topical administration of 5-FU. Our patient fits well with a recently published case report in which a potential interaction with uracil/tegafur and leflunomide was described by Kopp *et al.* [21].

The pathogenesis of peripheral neuropathy secondary to 5-FU is not clear [9,10,22,23]. 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 multifactorial. *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 with the release of carbon dioxide and ammonia [24]. Fluoro-β-alanine has a much slower clearance and a longer half-life than 5-FU.

The most prominent mutation of the DPD gene resulting in severe DPD deficiency is a G to A mutation in the GT 5′-splice recognition site of intron [8]. The carriers of the DPD exon 14-skipping mutation are at significantly increased risk of experiencing life-threatening myelosuppression upon 5-FU treatment, even when the allelic status is heterozygous [25]. These data have led to the suggestion of routine testing for the exon 14-skipping mutation before 5-FU treatment.

Sensorimotor polyneuropathy manifesting as symptoms of unsteady gait and reduced sensation in the legs has been reported as a side-effect of oral 5-FU, but not of topical 5-FU so far [9,10]. Few other cases have documented parenteral 5-FU as the cause of peripheral neuropathy [8]. 5-FU can also be responsible for optic nerve toxicity in patients with DPD deficiency [26]. Experimental neurotoxicity of 5-FU and its derivatives is documented, and is due to poisoning of neurons by the monofluorinated organic metabolites, monofluoroaceticacid and α-fluoro-β-alanine [27].

Our patient had been suffering from neuropathy for years and had tried medications for partial relief of symptoms. Finally, when his symptoms had alleviated due to dietary changes (reduced alcohol intake), a serious exacerbation occurred after the application of topical 5-FU. The data – that the onset of symptoms was preceded by topical 5-FU use; systemic 5-FU is known to cause peripheral neuropathy; his exacerbation occurred when he was clinically stable and applied 5-FU only; and no other manifestations of alcoholism were present – led us to believe that the topical form of 5-FU was responsible for the exacerbation of his sensory symptoms. The patient has normal DPD activity, hence the role of DPD deficiency was ruled out.

We recommend that family practitioners, internists and dermatologists be aware of this potential adverse effect of the topical form of 5-FU. If someone is already suffering from peripheral neuropathy, we suggest not starting this medication. The recommended current treatment for fluorouracil-induced neurotoxicity suggests oral thiamine supplementation in addition to stopping of the drug [28]. Further studies are indicated to confirm the association between topical 5-FU use and peripheral neuropathy.

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