Peripheral neuropathy associated with capecitabine

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5-Fluorouracil (5-FU)-associated peripheral neuropathy is an uncommon event. Capecitabine (CAP) is a pro-drug of 5-FU and peripheral neuropathy associated with CAP has not been reported. During analysis of 28 patients receiving CAP with concomitant radiation (XRT) for pancreatic cancer (resected or locally advanced), two patients developed signs and symptoms consistent with peripheral neuropathy. Patients received CAP 1200–1600 mg/m^2 in two divided doses with XRT (total 5040–5400 Gy) × 6 weeks, followed by 4 weeks rest, then 6 cycles of CAP 2000–2500 mg/m^2 in two divided doses × 14 days every (q) 3 weeks. Patients were assessed weekly during CAP-XRT and q 3 weeks during CAP alone. Patient A reported right leg weakness (foot drop) during week 4 of CAP-XRT (1600 mg/m^2). Patient B developed perioral and upper extremity paresthesias during the fourth cycle of CAP alone (2500 mg/m^2). Dihydropyrimidine dehydrogenase (DPD) activity was measured by radioisotopic assay using lysates of peripheral blood mononuclear cells. Neurologic examination revealed right foot drop in Patient A and was unremarkable in Patient B. Central nervous system imaging was negative. Electromyogram and nerve conduction studies showed sensorimotor peripheral neuropathy in both patients. DPD activity was normal in both patients. There was no evidence of disease progression. Neurologic symptoms resolved after stopping CAP for 4 weeks in Patient A, with no recurrence after reinitiating CAP alone at 2000 mg/m^2. Patient B continued at 80% of standard dose (2000 mg/m^2) and symptoms resolved without further intervention. We conclude peripheral neuropathy with 5-FU is rare. Neurotoxicity occurs most often with intermittent high dose 5-FU as bolus injection or 24- to 48-h infusions. The etiology of neurotoxicity in our two patients remains unclear; however, as CAP is rapidly metabolized to 5-FU in patients with normal liver function, it is likely that 5-FU or its active metabolites (fluoro-β-alanine) were contributing factors. Knowledge regarding potential adverse effects of CAP is paramount and dose modification is indicated with development of neurotoxicity. *Anti-Cancer Drugs* 15:767–771 © 2004 Lippincott Williams & Wilkins.

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Introduction

5-Fluorouracil (5-FU), an analog of uracil that has a fluorine atom at the 5′-position of the pyrimidine ring, was first used clinically as an anti-cancer agent over 40 years ago. It is the third most commonly used chemotherapy employed as a component of therapy for a variety of malignancies, including cancers arising in the head/neck, esophagus, stomach, colon, rectum, anus and breast. 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 initially described in the early 1960s. One of the most commonly described central nervous system (CNS) toxicities 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 [2–5]. Serious cognitive impairment such as difficulty concentrating, somnolence, coma and organic brain syndrome or dementia have also been seen. These symptoms are usually reversible upon discontinuation of the drug [1]. Neurologic toxicity has been reported most often with schedules that employ high intermittent doses of 5-FU given by either bolus injection or 24- to 48-h infusions, but has also been seen with intensive daily schedule. Peripheral neuropathy has been reported as a rare finding [6].

Peripheral neuropathy has been reported with capecitabine (CAP) 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 no prior report of peripheral neuropathy following administration of CAP. Herein, we describe the clinical and neurophysiological findings of two patients, and discuss the potential implications of this unusual toxicity in relation to CAP (Table 1).

CAP (Xeloda) was developed as a tumor-selective fluoropyrimidine carbamate to achieve higher intratumoral 5-FU level and lower toxicity than 5-FU [7]. CAP passes unchanged through the gastrointestinal tract and

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

Reference	Age/gender	5-FU/Xeloda (mg/m^2)	Concurrent chemotherapy/radiation	Neurotoxicity	Treatment	Outcome
Stein *et al.* [27]	71 male	450 i.v. push daily × 5	levamisole	pain in lower limbs	RTX discontinued	symptoms stabilized until the patient was rechallenged with 5-FU and leucovorin for liver metastasis; subsequent deterioration in neurotoxicity occurred requiring discontinuation of 5-FU/LV
Stein *et al.* [27]	54 female	450 i.v. push daily × 5	levamisole	pain and numbness in lower limbs	RTX discontinued	improved but incomplete resolution
Saif *et al.* [6]	65 male	65 p.o. days 1–3 weekly x 3 of 4 weeks	leucovorin + eniluracil	reduced sensation in leg leading to unsteady gait	5-FU dose reduced	symptoms stabilized with dose reduction; gradually improved after RTX stopped with persistent foot drop
Saif *et al.* [6]	70 male	23.4 p.o. days 1–3 weekly × 3 of 4 weeks	leucovorin + eniluracil	reduced sensation in leg leading to unsteady gait	5-FU dose reduced	symptoms stabilized with dose reduction; gradual but incomplete improvement after RTX stopped
Current case 1	65 male	1600 mg/m^2 in two divided doses × 6 weeks	radiation (5.4 cGy)	foot drop	CAP held; later reduced	improved but incomplete resolution
Current case 2	50 female	2500 mg/m^2 in two divided doses × 14 days q 21 days	none	perioral and bilateral tingling, numbness in hands	CAP dose reduced	symptoms resolved

is metabolized in the liver to 5′-deoxy-5-fluorocytidine (5′-DFCR). Here it is converted to doxifluridine (5′-DFUR) and, finally, 5′-DFUR is metabolized by thymidine phosphorylase to 5-FU at the tumor site [8]. Preclinical studies have demonstrated CAP's activity in both 5-FU-sensitive and 5-FU-resistant tumors [8]. The recommended dose and schedule of CAP is 2500 mg/m^2/day (total dose divided into two equal morning and evening doses) given in an intermittent schedule (2 weeks on/1 week off) [10]. Diarrhea and hand/foot syndrome are the principal toxicities [10,11].

Table 2 Sequence of events in two reported patients

Patient	Dose of capecitabine	Peripheral neuropathy grade (I–IV)
A	1600 mg/m^2 + XRT	grade III
	held doses (× 4 weeks)	resolved to grade I
	2000 mg p.o. b.i.d.	none (baseline: grade I)
	1650 mg p.o. b.i.d.	none (baseline: grade I)
B	1600 mg/m^2 + XRT	none
	2500 mg/m^2	grade II
	held doses (× 2 weeks)	resolved to grade I
	2000 mg/m^2	grade I resolved to none

Patients and methods

To date, 28 patients have received CAP with concomitant radiation (XRT) for pancreatic cancer (four resected or 24 locally advanced) at the University of Alabama at Birmingham. Patients received CAP 1200–1600 mg/m^2 p.o. b.i.d. with XRT (5040–5400 cG at 180 cGy per fraction delivered 5 days per week) over 6 weeks followed by 4 weeks rest, then 6–8 cycles of CAP 2000–2500 mg/m^2 p.o. b.i.d. × 14 days every (q) 3 weeks for the surgically resected patients and CAP 2000–2500 mg/m^2 p.o. b.i.d. × 14 days q 3 weeks until progressive disease for locally advanced unresected patients. Computed tomography (CT) image-based three-dimensional treatment planning was utilized to optimize radiation treatment planning by facilitating identification of the target volume and surrounding normal structures. Attempts were made to minimize radiation dose to surrounding normal tissues while ensuring adequate dose to the target volume. Patients were assessed weekly during CAP-XRT and q 3 weeks during CAP alone. Follow-up evaluations include toxicity assessments using NCI Common Toxicity Criteria, version 2.0, CT of the chest, abdomen and pelvis (RECIST criteria for response), complete blood counts, serum chemistries and CA 19-9. Two patients (7.1%) developed peripheral neuropathy and were continued at 80% of standard dose (2000 mg/m^2) with complete resolution of symptoms and no further intervention (Table 2).

Measurement of DPD activity

DPD activity was measured by an *ex vivo* radioisotopic assay using lysates of peripheral blood mononuclear cells as previously described [6,12].

Results

Twenty-eight patients (males, females) were treated on the schedule between September 2001 and December 2002. 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 histology was

pancreatic adenocarcinoma in 27 and neuroendocrine in one patient. Median follow-up time was 6.5 months (range 1–12.5 months).

Description of the two patients

Patient A

The first patient was a 65-year-old Caucasian male with adenocarcinoma of the pancreas. He underwent a Whipple's procedure with feeding jejunostomy. His past medical history was non-contributory, and the medications include reglan, zantac, colace, megace and pancrealipase. He has smoked about one pack of cigarettes per day for 50 years, but stopped at the time of diagnosis and denied alcohol abuse. His examination at the time of start of adjuvant CAP-XRT did not reveal any abnormality except a well-healed scar mark on the abdomen. His regimen included CAP (1600 mg/m^2 in two divided doses) with concurrent XRT (30 fractions; 5040 Gy).

He tolerated the therapy well for the first 4 weeks without any toxicity. At the start of the fifth week, he presented with an unsteady gait. The chemotherapy was stopped. Neurological evaluation revealed impaired heel–toe walking, diminished sensation to pinprick in the lower extremities and decreased distal motor strength. A magnetic resonance imaging 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}, thyroid-stimulating hormone (TSH), rheumatoid factor and thiamine levels were normal, and antibodies against double-stranded DNA, phospholipid and cardiolipin were negative. A nerve biopsy was suggested, but patient denied. 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. Evaluation by neurologist concurred with foot drop secondary to perineal nerve palsy. The patient's symptoms slightly improved with a 4-week treatment delay. After extensive discussion, the decision was made to restart chemotherapy and with careful follow-up of his neurologic status.

He received an additional 6 cycles with no clinical change or deterioration in neurological signs or symptoms. He received 2000 mg in two divided doses for 14 days every 21 days for the first 3 cycles and 1650 mg in two divided doses for the subsequent cycles (dose reduced due to hand/foot syndrome). No pharmacological measures except daily administration of vitamin B_6 (pyridoxine) at 300 mg/day was taken. The patient had gradual improvement in his gait, balance and coordination. Physical examination seven months after discontinuing revealed residual grade 2 sensory loss in the feet and grade 1 motor loss with dorsiflexion.

Patient B

The second patient was a 50-year-old white female who underwent a Whipple's procedure for pancreatic adenocarcinoma. Her only other medical problems included Meniere's disease, and medications were triamterene, viokase, reglan and zantac. She never smoked or abused alcohol.

Her examination at initiation of adjuvant chemoradiotherapy was normal. She received CAP at 1600 mg/m^2 in two divided doses Monday–Friday (weekends off) with concurrent radiation for 6 weeks with XRT followed by a 4-week break. Then, she re-initiated CAP at 2500 mg/m^2 in two divided doses $\times$ 14 days every 21. She tolerated first 3 cycles very well, but during the second week of the fourth cycle she developed tingling and numbness in both hands. 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 upper extremities. A magnetic resonance imaging 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 in the left upper extremity 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 abnormality. Restaging CT scans showed no evidence of disease progression and the patient wished to remain on the treatment dose (20% reduction = 2000 mg/m^2 in two divided doses). Based on the data supporting the role of vitamin B_6 (pyridoxine) therapy in patients having carpal tunnel syndrome, she was treated with 300 mg daily (100 mg p.o. t.i.d.). The patient received two additional complete cycles with no worsening of her symptoms. Clinical evaluation 3 months later indicated subjective improvement as well as improvement in the sensory loss in upper extremities.

Discussion

Capecitabine, through a series of enzymatic steps, the final step being catalyzed by the action of thymidine phosphorylase is converted to 5-FU [7–10]. Since many tumor tissues contain higher levels of this enzyme compared to normal tissues, formation of 5-FU may occur preferentially within tumor tissue [8–10]. CAP has been approved by FDA for use in colorectal cancer as well as breast cancer. Its use in pancreatic cancer has also shown promising results in a phase II study by Cartwright [13]. Clinical safety data is available in thousands of patients with either breast or colorectal cancer enrolled in

different clinical trials. The most commonly used schedule includes 2500 mg/m^2 daily for 2 weeks followed by a 1-week rest period. The most commonly reported toxicities included hand/foot syndrome (57%), diarrhea (57%), nausea (53%) and vomiting (37%). Overall, grade 3–4 toxicities of the following types were observed: diarrhea, 13%; nausea/vomiting, 4%; stomatitis, 4%; abdominal pain, 4%; constipation, 1%; anorexia, 2%; dehydration, 3%; hand/foot syndrome, 13%; fatigue, 5%; neutropenia, 5%; thrombocytopenia, 2%; anemia, 3%; lymphopenia, 46%; hyperbilirubinemia, 17% [10,11,13]. Neurological side-effects associated with CAP have not been reported independently.

Neurological side-effects associated with bolus administration of 5-FU were first reported as cerebellar ataxia in 1964 by Moertel *et al.* and Riehl and Brown [2,3]. Since 1964, other investigators have reported CNS toxicity with a variety of 5-FU schedules. Although the dose-limiting CNS toxicity is rare, the frequency seems to be related to the dose and schedule of 5-FU, as well as concurrent use of other chemotherapy agents. Acute encephalopathy may manifest as insomnia, difficulty concentrating, confusion, stupor or coma. Cerebellar findings may range from simple gait ataxia to a more florid pan-cerebellar syndrome associated with global motor weakness, bulbar palsy, bilateral oculomotor nerve palsy and upper motor neuron signs. These symptoms are usually reversible upon discontinuation of 5-FU [14]. 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. We previously reported two patients who developed peripheral neuropathy while receiving oral 5-FU with eniluracil [6]. Peripheral neuropathy associated with capecitabine, a pro-drug of 5-FU, has not been reported.

The etiology of peripheral neuropathy in our two patients is not clear; however, as CAP is rapidly metabolized to 5-FU in patients with normal liver function, it is likely that 5-FU or its active catabolites may be the contributing factors, such as FBAL. *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 [15–17]. 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 [18,19].

Preclinical models suggest a biochemical basis for neurological toxicity probably related to 5-FU catabolites [20–25]. Exposure of cerebellar cultures established from brains of one-day old mice to concentrations of either 7 or 70 μM FBAL or fluoroacetate resulted in selective concentration- and time-dependent injury to myelin, with sparing of the oligodendrocytes and neurons [20]. On the other hand, exposure to 7 μM of either the two physiological counterparts, β-alanine and acetic acid, or to 5-FU, did not produce injury to myelin fibers [17]. Following systemic administration of radiolabeled FBAL to rats, prolonged accumulation of [^{3}H]FBAL occurs in brain tissues [16]. Berg *et al.* administered 10 mg 5-FU intraventricularly to rhesus monkeys and found no clinical signs of neurotoxicity, even though the peak ventricular concentrations exceeded 10 mM [25]. In contrast, intralumbar administration of the same 5-FU dose led to delayed onset of bilateral hind limb paralysis. Histopathologic changes at necropsy revealed demyelination of the lumbar and sacral cords and severe necrosis of the ventral horn of the sacral spinal cord [25]. Other investigators have reported that the deoxyribonucleoside metabolite of 5-FU, fluorodeoxyuridine, can be safely administered to rats by the intrathecal route [26]. 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 [26].

Knowledge regarding potential neurotoxicity manifesting as peripheral neuropathy associated with CAP is paramount and dose modification is indicated with development of neurotoxicity. Anecdotal reports suggested that thiamine administration may ameliorate acute Wernicke–Korsakoff-like encephalopathy [19] and, in one DPD-deficient patient, a continuous i.v. infusion of thymidine was associated with recovery from 5-FU-associated coma [12]. Treatment with vitamin B_6 (pyridoxine) for a minimum period of 12 weeks, depending upon the duration and severity of the symptoms, has been effective without surgery in few small studies in patients with idiopathic carpal tunnel syndrome [28]; however, the role of vitamin B_6 is not known in ameliorating peripheral neuropathy.

In summary, we describe two patients with no known predisposing factors who developed signs and symptoms of peripheral sensorimotor neuropathy while receiving capecitabine. Although we did not perform pretreatment neurophysiological studies in the two patients reported herein, neither had symptoms of peripheral neuropathy at the start of treatment and the neurologic exam done as part of the pretherapy physical examination was unremarkable. However, no other patients have experienced signs or symptoms of peripheral neuropathy. We did not find deficiency of DPD activity in these two patients. Although the etiology of peripheral neuropathy related to 5-FU or its related drugs may be multifactorial, we suggest that since CAP is a pro-drug of 5-FU, it is likely that 5-FU itself, or most probably its active metabolite (FBAL), was the contributing factor. Although symptoms

of unsteady gait complicating fluoropyimidines therapy is 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, CAP dose reduction should be considered.

References

1 Shehata N, Pater A, Tang SC. Prolonged severe 5-fluorouracil-associated neurotoxicity in a patient with dihydropyrimidine dehydrogenase deficiency. *Cancer Invest* 1999; **17**:201–205.

2 Riehl JL, Brown WJ. Acute cerebellar syndrome secondary to 5-fluorouracil therapy. *Neurology* 1964; **14**:961–967.

3 Moertel CG, Reitemier RJ, Bolton CF, Shorter RG. Cerebellar ataxia associated with fluorinated pyrimidine therapy. *Cancer Chemother Rep* 1964; **41**:15–18.

4 Lynch HT, Droszcz CP, Albano WA, Lynch JF. 'Organic brain syndrome' secondary to 5-fluorouracil toxicity. *Dis Colon Rectum* 1981; **24**:130–131.

5 Moore DH, Fowler WC, Crumpler LS. 5-Fluorouracil neurotoxicity. *Gynecol Oncol* 1990; **36**:152–154.

6 Saif MW, Wilson RH, Harold N, Keith B, Dougherty DS, Grem JL. Peripheral neuropathy associated with weekly oral 5-fluorouracil, leucovorin and eniluracil. *Anticancer Drugs* 2001; **12**:525–531.

7 Ishikawa T, Utoh M, Sawada N, Nishida M, Fukase Y, Sekiguchi F, Ishitsuka H. Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts. *Biochem Pharmacol* 1998; **55**:1091–1097.

8 Bajetta E, Carnaghi C, Somma L, Stampino CG. A pilot safety study of capecitabine, a new oral fluoropyrimidine, in patients with advanced neoplastic disease. *Tumori* 1996; **82**:450–452.

9 Dooley M, Goa KL. Capecitabine. *Drugs* 1999; **58**:69–76; Discussion 77–78.

10 Mackean M, Planting A, Twelves C, *et al.* Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. *J Clin Oncol* 1998; **16**:2977–2985.

11 Twelves C, Harper P, Van Cutsem E, *et al.* A Phase III trial of Xeloda (capecitabine) in previously untreated advanced/metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 1999; **18**:263a (abstr 1010).

12 Takimoto CH, Lu ZH, Zhang R, *et al.* Severe neurotoxicity following 5-fluorouracil-based chemotherapy in a patient with dihydropyrimidine dehydrogenase deficiency. *Clin Cancer Res* 1996; **2**:477–481.

13 Cartwright TH, Cohn A, Varkey JA, *et al.* Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. *J Clin Oncol* 2002; **20**:160–164.

14 Bygrave HA, Geh JI, Jani Y, Glynne-Jones R. Neurological complications of 5-fluorouracil chemotherapy: case report and review of the literature. *Clin Oncol (R Coll Radiol)* 1998; **10**:334–336.

15 Liaw CC, Wang HM, Wang CH, *et al.* Risk of transient hyperammonemic encephalopathy in cancer patients who received continuous infusion of 5-fluorouracil with the complication of dehydration and infection. *Anticancer Drugs* 1999; **10**:275–281.

16 Yeh KH, Cheng AL. High-dose 5-fluorouracil infusional therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy. *Br J Cancer* 1997; **75**:464–465.

17 Akiba T, Okeda R, Tajima T. Metabolites of 5-fluorouracil, alpha-fluoro-beta-alanine and fluoroacetic acid, directly injure myelinated fibers in tissue culture. *Acta Neuropathol (Berl)* 1996; **92**:8–13.

18 Pirzada NA, Ali II, Dafer RM. Fluorouracil-induced neurotoxicity. *Ann Pharmacother* 2000; **34**:35–38.

19 Langer CJ, Hageboutros A, Kloth DD, Roby D, Shaer AH. Acute encephalopathy attributed to 5-FU. *Pharmacotherapy* 1996; **16**:311–313.

20 Bourke RS, West CR, Chheda G. Kinetics of entry and distribution of 5-fluorouracil in CSF and brain following intravenous injection in a primate. *Cancer Res* 1973; **33**:1735–1746.

21 Davis ST, Joyner SS, Baccanari DP, Spector T. 5-Ethynyluracil (776C85): protection from 5-fluorouracil-induced neurotoxicity in dogs. *Biochem Pharmacol* 1994; **48**:233–236.

22 Okeda R, Shibutani M, Matsuo T, Kuroiwa T, Shimokawa R, Tajima T. Experimental neurotoxicity of 5-fluorouracil and its derivatives is due to poisoning by the monofluorinated organic metabolites, monofluoroacetic acid and alpha-fluoro-beta-alanine. *Acta Neuropathol (Berl)* 1990; **81**: 66–73.

23 Okeda R, Shibutani M, Matsuo T, Kuroiwa T. Subacute neurotoxicity of 5-fluorouracil and its derivative, carmofur, in cats. *Acta Pathol Jpn* 1988; **38**:1255–1266.

24 Neuwelt EA, Glasberg M, Frenkel E, Barnett P. Neurotoxicity of chemotherapeutic agents after blood–brain barrier modification: neuropathological studies. *Ann Neurol* 1983; **14**:316–324.

25 Murphy RF, Poplack DG. Intrathecal 5-fluorouracil in the rhesus monkey. *Cancer Chemother Pharmacol* 1992; **31**:127–130.

26 Yamada M, Nakagawa H, Fukushima M, Shimizu K, Hayakawa T, Ikenaka K. *In vitro* study on intrathecal use of 5-fluoro-2-deoxyuridine (FdUrd) for meningeal dissemination of malignant brain tumors. *J Neurooncol* 1998; **37**:115–121.

27 Stein ME, Drumea K, Yarnitsky D, Benny A, Tzuk-Shina T. A rare event of 5-fluorouracil-associated peripheral neuropathy: a report of two patients. *Am J Clin Oncol* 1998; **21**:248–249.

28 Ellis J, Folkers K, Levy M, *et al.* Therapy with vitamin B_6 with and without surgery for treatment of patients having the idiopathic carpal tunnel syndrome. *Res Commun Chem Pathol Pharmacol* 1981; **33**:331–344.