study, patients with CA125 levels greater than 35 U/ml after two courses of treatment have a mortality at 12 months of 85%. In such patients, the use of further active therapy is questionable and the identification of this subgroup would reduce unwarranted toxicity. It is possible that CA125 levels at an earlier point, such as after only one course of treatment, may yield equally useful but more timely information.

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Interferon-related Mental Deterioration and Behavioral Changes in Patients with Renal Cell Carcinoma

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Five out of 38 patients (13%) with metastatic renal cell carcinoma had mental deterioration 3 weeks to 13 months after the start of treatment with recombinant interferon alpha-C. Metastatic spread to the brain, paraneoplastic effect of the tumor on the central nervous system and other causes of dementia were excluded. Computed tomography of the brain in these patients was normal and the width of the cerebral sulci and ventricles did not correlate with the severity of dementia. Specific patterns of atrophy were not seen. General deterioration, assessed by the change in Karnofsky performance status, was associated with dementia. The dementia may have been caused by a neurotoxic effect of interferon.
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INTRODUCTION

MENTAL DETERIORATION in patients with cancer constitutes a diagnostic challenge since it may be due to different etiologies and has a major impact on further treatment planning. Various etiologies underlie the appearance of dementia and behavioral changes in these patients, such as metabolic derangements, paraneoplastic phenomena, metastatic spread to the brain, and iatrogenic causes, including damage following radiation, chemotherapy and interferon therapy [1–6]. The diagnostic approach to define the exact etiology in the complex cancer patient may be difficult. Imaging is helpful in differentiating between the various causes of dementia [7–11]. We present five patients with metastatic renal cell carcinoma (RCC) treated by recombinant interferon alpha-C who deteriorated mentally while being treated.

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PATIENTS AND METHODS

Patient population

Thirty-eight patients with metastatic RCC with no apparent mental or behavioral derangement were treated with recombinant interferon alpha-C (highly purified bacteria-derived inter-

Table 1. Patients' data and treatment

Patient	Primary excised	Sites of metastases	Treatment		
			Interferon	Dose	Period
1 (M/65)	+	Lungs	1 alpha-C	3–6 MU every 2 days	1.5 mo
		Lymph nodes	2 alpha-C	12 MU every 2 days	
			+vinblastine	0.1 mg/kg every 3 wk	3 mo
2 (M/69)	+	Thigh	1 alpha-C	3–6 MU every 2 days	2.5 mo
		Gluteus	2 alpha-C	18 MU every 2 days	
			+vinblastine	0.1 mg/kg every 3 wk	3 mo
3 (M/75)	−	Kidney	alpha-C	3–6 MU every 2 days	3 wk
		Lymph nodes			
4 (M/60)	+	Local rec.	alpha-C	3–6 MU every 2 days	3 mo
		Liver bones			
5 (M/70)	+	Liver	alpha-C	3–6 MU every 2 days	2 mo

feron with a specific activity of 1–2 × 10^9 U/mg protein; Interpharm Ltd., Ness-Ziona, Israel). Five male patients (13%) in whom mental deterioration was observed were investigated (age range 60–75 years, median 69). Metastatic sites included liver (2 patients), lymph nodes (2), lungs (1), muscles and bones (2) and kidneys (2). All had Karnofsky performance status of 90% and none had any sign of brain metastases or neurological and cognitive dysfunction. Previous treatments included nephrectomy only (one patient) and nephrectomy followed by hormone therapy or chemotherapy for recurrent or metastatic disease (three patients). One patient had not been treated.

Recombinant interferon alpha-C was administered in accordance with the following schedule: patients 1–4 started on 3 × 10^6 U daily for 14 days and then 3 × 10^6 U/m^2 every second day until the disease progressed. One patient (number 5) started on 3 × 10^6 U daily for 7 days and then the dose was gradually escalated up to 10 × 10^6 U/m^2 every second day until the disease progressed. All five patients failed to respond. Progression of disease was observed within 1.5–3 months following the introduction of treatment by interferon in all patients. Two patients (1 and 2) received further recombinant interferon alpha-C, 12–18 × 10^6 U every second day, together with vinblastine 0.1 mg/kg intravenously every 21 days for 2.5 and 3 months, respectively, as second line treatment, but again failed to respond. None of the patients received corticosteroid therapy during interferon treatment. All patients received nutritional supplements to ensure adequate protein and calorie intake. They developed mental and cognitive deterioration evaluated by oncologists and neurologists. Leptomeningeal carcinomatosis was excluded by clinical examination, cerebrospinal fluid (CSF) analysis and computed tomography (CT). Patients' data and treatment are summarized in Table 1.

Methods

Evaluation of physical status was based on the following criteria: body weight, performance status, serum levels of cholesterol, total proteins and albumin within 24 h before and after cessation of interferon treatment. Severity of weight loss was assessed [12]. Metabolic disorders were excluded by the normal values of serum calcium and electrolytes, liver enzymes, renal function tests, and thyroid hormones. All the patients in whom mental deterioration was observed underwent a thorough neuropsychiatric evaluation which consisted of an interview, neurological and mental status examination. We checked the patient's orientation, registration, attention, calculation, memory, language, writing, reading, copying, performance of orders and understanding of sentences. Neurological examination, CSF analysis and CT of the brain, with and without intravenous injection of contrast material, ruled out metastatic spread to the brain.

Subjective inspection of CT scans was done by one author (I.R.G.) to evaluate possible changes in the gray and white matter of the brain. In addition, linear measurements of CSF spaces were performed and included: ventricular score (VS) and sulcal score (SS) [13] and bifrontal (CVI-1) and bicaudate (CVI-2) cerebroventricular indices [14].

Table 2. Physical deterioration

Patient	Period (mo)	Weight loss [kg per mo (%)]	Percentage decrease in serum			Performance status (%)	
			Cholesterol	Protein	Albumin	Before	After
1	4	2.5 (13)	30.5	27.0	27.0	90	70
2	6	1.6 (14)	5.0	15.5	27.0	90	60
3	1	10.0 (15)	15.5	25.0	39.0	90	40
4	1.5	— —	11.5	6.5	—	90	50
5	2	13.0 (28)	24.0	13.0	30.5	90	40

Table 3. CNS toxicity

Patient	Cognitive disorder*	Mood	Lethargy	Confusional state	Reversibility of symptoms	Death	Neurological findings	CSF analysis
1	Mild	Depression Lack of initiative	Moderate	Mild	Complete	–	Normal	Normal
2	Moderate	Aggressive	Moderate	Moderate	Complete	–	Normal	Normal
3	Severe	Lack of initiative	Severe	Severe	None	+	Ataxia, apraxia, disorientation, poor coordination, cortical blindness	Normal
4	Moderate	Aggressive	Moderate	Mild	Partial	–	Normal	Normal
5	Severe	Depression	Severe	Severe	None	+	Normal	Normal

*Memory, concentration, writing, reading.

RESULTS

The overall response to recombinant interferon alpha-C in the initial group of thirty-eight patients was 8% and was partial. The mean duration of the partial response was 5.6 months. Disease stabilization was achieved in 24% of patients who had progressive disease before interferon administration for a mean duration of 5.8 months. Five patients showed mental deterioration. Fatigue and weakness without mental deterioration were observed in another six patients.

Physical deterioration was found in the five patients showing central nervous system (CNS) toxicity (Table 2). All patients started interferon treatment with a performance status of 90% and deteriorated 40–70% within 1–6 months (median 2 months). Weight loss was severe (10% of body weight or more) in four patients and mild in one. The rate of weight loss was 10 kg/month or more in two patients (3 and 5). Serum level of cholesterol was reduced by 5–30.5% of the baseline level. Total serum protein level fell by 6.5–27%, and serum albumin level fell by 0–39% of the initial level. Similar changes in laboratory values were observed also in seven patients without mental deterioration.

CNS toxicity was observed within 3 weeks to 3 months after introduction of interferon treatment (Table 3). All patients had disturbances in recent memory, reading, writing and concentration. Behavioral and emotional changes included depression, agressiveness and lack of initiative. Lethargy and a state of confusion were observed in all patients. Coma and death within 1 month after cessation of treatment occurred in two patients. Additional neurological findings included ataxia, apraxia, poor coordination and cortical blindness in one patient. Mental changes were not observed in another six patients who had similar changes in performance status while being treated with interferon.

CT revealed atrophy in three patients and periventricular white matter lucency in two. The severity of dementia was not associated with degree of atrophic changes (Fig. 1). The ventricular scores and indices are presented in Table 4.

Table 4. CT findings and morphometric study

Patient	CT	CVI-1*	CVI-2*	Ventricular score	Sulcal score
1	Atrophy in posterior fossa	35.1	22.0	65.0	2.9
2	Atrophy and PVL*	39.6	25.0	81.4	2.9
3	Atrophy and PVL*	22.9	19.5	43.5	3.7
4	Normal	43.3	23.4	71.2	3.3
5	Normal	34.7	17.5	48.8	3.7

*CVI-1 and CVI-2 = cerebroventricular indices; PVL = periventricular lucency.

DISCUSSION

The appearance of mental and behavioral changes in our patients was attributed to the interferon treatment rather than to the primary disease. These effects occur in about one-third of interferon treated patients, being severe in only 7% [15]. The adverse reactions to interferon include somnolence and confusion, fatigue, lethargy, psychiatric symptoms and anorexia, reducing the patients to a catabolic state. The more severe derangements include conceptual disorganization, neurological deficits and coma [4, 16–19]. These effects are generally reversible [5, 15, 16]. The mode of action of interferon on the central nervous system is not fully understood, and possible mechanisms include competition on membrane receptors with neurotropic hormones such as thyrotropin and endorphin-like opioid effects [16, 20, 21]. Toxic effects of interferon on the brain are widely described, and occur in cancer patients earlier than in patients with other diseases [4, 5, 19, 22]. The incidence of interferon toxicity on the central nervous system is related to dose and the age of patients [15, 23]. In our study the more severe symptoms occurred in older patients and within a shorter period after the introduction of interferon treatment. The median age of our patients was 69 years, which is higher than in the other series [4, 5]. The association between patients' age and onset of these toxic symptoms has not been referred to in the above mentioned references. Similarly, there are no data in the literature cited linking between the site and type of the primary malignant process and the interferon toxicity. In the case described by Laaksonen *et al.* [3] the dementia occurred in a patient with small cell lung cancer treated by interferon for more than 2

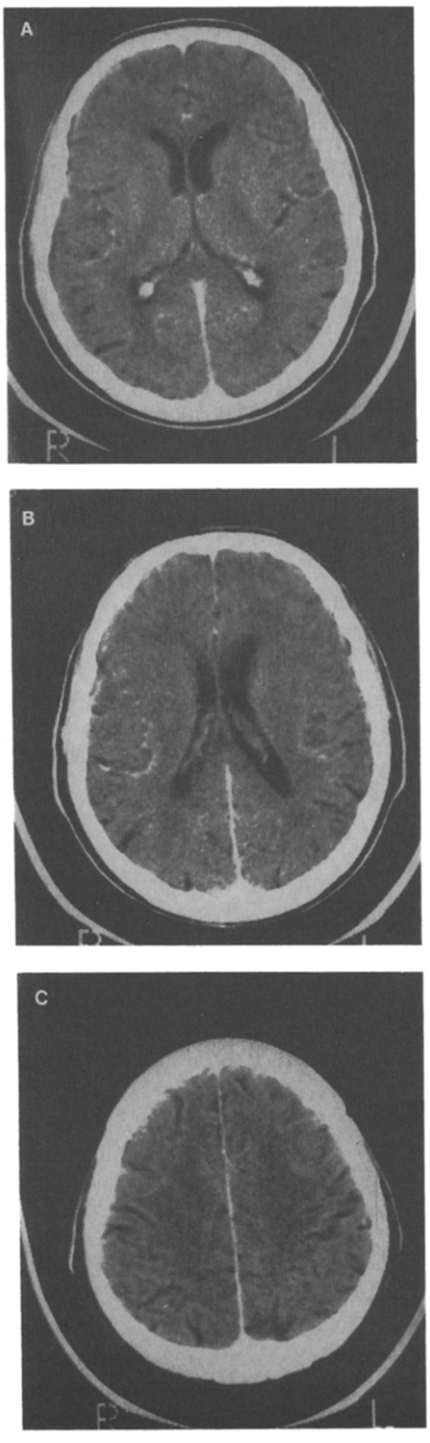

Fig. 1. CT in patient 5. Third ventricle (A) and lateral ventricles (B) are normal. Sulci (C) show mild widening.

years, 2 months following cranial irradiation [3]. Dementia could be part of a paraneoplastic syndrome in lung cancer and follows brain irradiation; therefore, the relationship between interferon treatment and dementia in this patient cannot be isolated and is uncertain [1, 2]. In our series, interferon was the only treatment given to patients close to the onset of dementia. Since metastatic lesions or vascular changes in the brain were not demonstrated by CT, and paraneoplastic CNS effects of RCC are not described, the association between dementia and the interferon treatment in our patients is most probable. This association is also supported by the fact that cessation of treatment resulted in complete reversal of dementia in two patients. The fact that significantly smaller ventricles (as reflected by ventricular score) were found in the more severely demented patients, supports the hypothesis of neurotoxicity of interferon rather than structural changes in the brain in these patients. The values obtained for ventricular score and sulcal score did not relate to the mental state of the patients. The general deterioration, as reflected by the change in performance status in our patients, decrease in serum albumin level and rate of weight loss, correlated with the severity of dementia. It could be that the general deterioration reflected the overall toxicity of the interferon [15]. Progression of the disease as explanation for physical deterioration is less likely. The course of the disease in these patients was not fulminant, and the measurable changes in metastases during the period of treatment were small compared with the striking changes in physical parameters. The association between the general toxicity and the neurotoxicity of interferon has to be clarified in larger series.

Recombinant interferon alpha-C may be neurotoxic in RCC patients leading to dementia. Behavioral and mental changes are warning signs and treatment should be withdrawn.

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Effect of CGS 16949A plus Tamoxifen on Induced Mammary Tumours in Rats

T. Tominaga, Y. Yoshida, K. Shimozuma, K. Hayashi and G. Kosaki

The antitumour effect of CGS 16949A, an aromatase inhibitor, was investigated in rats with mammary tumours induced by 7,12-dimethylbenz[a]anthracene. A dose-dependent antitumour effect was observed after daily oral administration of CGS 16949A for 3 weeks. The tumour did not recur in the groups treated with 4.0 and 8.0 mg/kg per day. The complete remission rate increased and the time required to achieve complete remission became shorter with increasing daily doses. After daily administration for 3 weeks, a significant antitumour effect was observed in the group treated with CGS 16949A plus tamoxifen compared with that seen either with CGS 16949A or with tamoxifen alone. At the end of treatment, the group treated with CGS 16949A had significantly decreased oestradiol-17β and prolactin levels and increased levels of follicle stimulating hormone, but oestrone was not affected.
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INTRODUCTION

THE ROLE of oestrogens in the initiation and promotion of breast cancer has long been recognized [1]. The growth of breast cancer can also be inhibited by the deprivation of oestrogens via blockade of synthesis of oestradiol or its precursors [2]. Endocrine therapy has been widely used to reduce the amount of oestradiol acting locally on the tumour. Gonadotropin-releasing hormone (GnRH) analogues [3–5] which inhibit the release of LH and FSH, and aromatase inhibitors [6, 7], which inhibit steroid biosynthesis, are attracting attention.

Similarly to several other steroidogenic enzymes, aromatase is cytochrome P-450 dependent [8]. The first, clinically useful aromatase inhibitor, aminoglutethimide, not only reduces the amount of circulating oestrogens by inhibiting aromatase but also inhibits adrenal steroidogenesis. It is also an androgen antagonist [9]. Trials of aminoglutethimide to block aromatase in postmenopausal patients with breast cancer showed efficacy similar to that following surgical adrenalectomy, but central nervous system and dermatological side-effects are substantial [10]. Because of aminoglutethimide's action, glucocorticoids have to be co-administered.

CGS 16949A is a nonsteroidal competitive inhibitor of aromatase that has shown higher potency and greater specificity in inhibition of aromatase than aminoglutethimide [6, 11]. We have studied the antitumour effect of CGS 16949A alone and combined with tamoxifen in rats with oestrogen-dependent mammary tumours.

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MATERIALS AND METHODS

Female Sprague–Dawley rats about 8 weeks old and weighing 180–200 g were used. 7,12-Dimethylbenz[a]anthracene (7,12-DMBA) was dissolved in olive oil (20 mg/ml), and was orally administered to 120 rats as a single dose of 100 mg/kg. After 8–12 weeks, 70 rats, whose mammary tumours measured 0.8–1.2 cm at their widest diameter, were selected and used for the experiment [12].

Tumour size and body weight were measured before treatment and weekly thereafter. Drugs were administered orally once daily for 3 weeks. Animals received a suitable diet (F2) and water freely.

At the end of treatment and at the end of the experiment (6 weeks), the animals were killed and the ovaries, uterus and adrenals were removed and weighed. At the same time, serum levels of oestradiol-17β, oestrone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) and prolactin were measured by radioimmunoassay.

Tumour size (cm^2) was defined as the product of the widest diameter and the greatest diameter perpendicular to it, and was expressed as the percentage of the initial size measured on day 0.

CGS 16949A was supplied by Ciba-Geigy and tamoxifen by ICI. CGS 16949A was dissolved in physiological saline and tamoxifen was suspended in 5% sodium carboxymethylcellulose (CMC-Na).