Eur J Cancer, Vol. 29A, No. 10, pp. 1497–1498, 1993.
Printed in Great Britain
0964–1947/93 $6.00 + 0.00

Cortical Blindness and Seizures Following Cisplatin Treatment : Both of Epileptic Origin?

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PERIPHERAL NEUROPATHY is a well-known dose-dependent side-effect of cisplatin. Cortical blindness is a less common but earlier described complication of cisplatin therapy.

We report 3 patients treated with cisplatin who experienced cortical blindness, which in 2 of them was associated with hypomagnesaemia.

Patient A was a 17-year-old boy who presented with a large mediastinal teratocarcinoma, for which he was initially treated with first- and second-line cisplatin-based chemotherapy. However, tumour mass was not reduced and a debulking surgical procedure was performed. Twelve days after the first postoperative cisplatin-based chemotherapy course he experienced bilateral visual loss and progressive lethargy. Neurological examination revealed normal pupil reactions to light, normal fundus and absence of optokinetic nystagmus and of reflex lid closure to threat, suggesting cortical blindness. The next morning he had a secondary generalised seizure. A computer tomography (CT) scan did not show intracerebral abnormalities. Sodium and potassium levels were normal, but hypomagnesaemia was present. He fully recovered from neurological dysfunction and his visual function normalised. One month later he died from progressive disease.

Patient B was a 25-year-old man who presented with a choriocarcinoma of the right testis and multiple metastases in lungs and para-aortal lymph nodes in November 1984. An extremely high β human chorianic gonadotrophin (HCG) level (> 500 000 U/l) was found. After an initial favourable response to cisplatin-based chemotherapy, βHCG level increased and second-line cisplatin-based chemotherapy was started. However, in May 1985, βHCG levels rose again. It was decided to treat him with high-dose chemotherapy, involving cyclophosphamide and etoposide, with subsequent autologous bone marrow transplantation (22 July 1985).

On 16 August 1985 the patient experienced sudden visual loss, preceeded by rhythmic jerking of the left arm with subsequent hemiparesis. Optokinetic nystagmus and reflex lid closure to threat were both absent. CT scan of the brain and blood chemistry were normal, except for a hypomagnesaemia (Mg = 0.73 mmol/l). Within 5 days all signs resolved spontaneously and he was discharged from the hospital. Shortly thereafter he died from a severe intraabdominal tumour-related haemorrhage.

Table 1. 3 cisplatin-treated patients with cortical blindness

Patient	Age (years)	Body surface area (m^2)	Cumulative cisplatin dose (mg)	Interval between last dose and blindness (days)	Mg^{2+} levels* (mmol/l)
A	17	2.0	1400	12	0.54
B	25	1.9	1680	92	0.73
C	50	2.1	700	14	1.07

* Normal range = 0.85 – 1.00 mmol/l.

Patient C is a 50-year-old man who started treatment with cisplatin in February 1992 for advanced adenocarcinoma of the lung. One week after the fifth cisplatin dose he presented with fever, diarrhoea and malaise. Culture of stools disclosed *Campylobacter jejuni* and erythromycin 4 × 500 mg intravenously was started. The patient subsequently developed a headache and 7 days after admission he complained of loss of vision in both eyes. No other neurological signs or symptoms were found. A CT scan of the brain was normal. The next morning he suffered from a generalised seizure. Serum calcium, potassium and magnesium levels were normal. After 2 days he was able to see blurred shapes and again 2 days later his vision had normalised.

In September 1992 he complained of blurred vision and headaches. A CT scan of the brain this time showed two ring-shaped enhancing intraparenchymal lesions in the left and right hemisphere.

Cisplatin neurotoxicity is not limited to the peripheral nervous system but can also be manifested as focal encephalopathy. The clinical picture consists of focal or generalised seizures, aphasia, hemiparesis and cortical blindness [4]. The 3 patients we describe were all treated with high-dose cisplatin regimens. They experienced visual loss due to cisplatin toxicity.

In 2 of our patients a hypomagnesaemia was found on the day of visual loss. Cisplatin is known to induce a renal tubular defect in magnesium conservation leading to serious clinical syndromes of magnesium deficiency [5]. Gorman *et al.* [4] also found hypomagnesaemia in 3 of 4 patients with focal encephalopathy associated with cisplatin. Like cisplatin, cyclosporin has nephrotoxic and neurotoxic side-effects. An association has been found between the neurotoxicity due to cyclosporin and the presence of hypomagnesaemia [6]. Cortical blindness has also been observed in a patient with cyclosporin toxicity [7]. Possibly, tubular dysfunction caused by either cyclosporin or cisplatin resulting in renal magnesium wasting and subsequent hypomagnesaemia increases the susceptibility of brain parenchyma to the neurotoxic effects of both drugs. This neurotoxicity can become manifest as seizures or as focal encephalopathy. When such neurotoxicity leads to epileptic activity in the occipital cerebral cortex, the patient can experience transient blindness either as an epileptic or as a postepileptic (postictal) phenomenon. Pippitt *et al.* [8] described a patient similar to ours, who indeed had focal epileptic activity on electroencephalogram during blindness. As a result of the enhanced vulnerability of the patient's brain, focal or generalised seizures can further complicate the clinical picture. The temporal association of cortical blindness with other (focal) epileptic manifestations and its

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Revised 18 Jan. 1993; accepted 2 Feb. 1993.

sudden onset suggest that it is the result of an epileptic manifestation. The predilection of the susceptibility of the occipital cortex for the neurotoxic effects of both cisplatin and cyclosporin remains unexplained. Adults, but even more so children, with hypomagnesaemia, high cumulative cisplatin doses and fever are at risk for the development of this sequence of events [9]. In view of the probable role of hypomagnesaemia, magnesium loss should be prevented and hypomagnesaemia be corrected. Generalised epileptic seizures often develop and short-term anticonvulsive treatment in these patients may be indicated.

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Eur J Cancer, Vol. 29A, No. 10, p. 1498, 1993.
Printed in Great Britain
0964–1947/93 $6.00 + 0.00
Pergamon Press Ltd

Survival Data Relating to the Use of Goserelin Depot in the Treatment of Premenopausal Advanced Breast Cancer

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WE WISH to report survival data for 228 pre- and perimenopausal advanced breast cancer patients treated with goserelin (Zoladex, ICI) in a programme of clinical studies which have been previously reported [1].

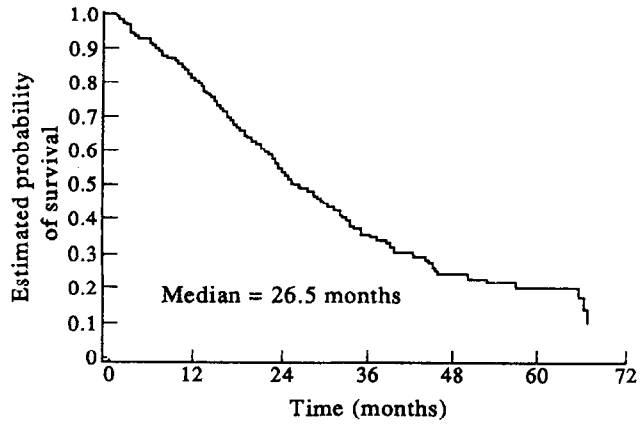

Fig. 1. Overall survival.

Using a Kaplan–Meier life table analysis for all patients (Fig. 1), the median survival time was 26.5 months (range 0.8–69.0). At the time of the data cut-off for the analysis, which was 5 April 1991, there were 153 deaths and 75 censored values. The censored values include 51 patients who were alive at the date of data cut-off and 24 patients who were lost to follow-up and who were 'alive' at the time of their last recorded visit to the trialist.

Tumour oestrogen receptor (ER) status was predictive of survival. The median survival time was 33.1 months (range 0.8–69.0) for ER-positive patients, 15.9 months (range 1.0–44.4) for ER-negative patients and 28.8 months (range 0.9–67.9) for those patients of unknown status.

Best objective response was predictive of survival. The median survival time for responders (i.e. patients who had a complete or partial regression of their disease on therapy) was 39.3 months (range 5.1–69.0) and for patients with stable disease the median survival time was 23.7 months (range 0.9–62.0). For patients who only showed progression the median survival time was 7.8 months (range 0.8–65.7).

These data compare favourably with the reported survival times for other hormonal therapies such as oophorectomy [2] and tamoxifen [3, 4] in premenopausal advanced breast cancer patients, thus confirming a role for the use of goserelin in the treatment of this patient population.

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Received 18 Feb. 1993; accepted 1 Mar. 1993.

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Acknowledgements—ICI Pharmaceuticals provided goserelin depot ("Zoladex") and grant support. Zoladex is a trade mark, the property of Imperical Chemical Industries plc.