Cancer Chemother Pharmacol (1986) 16: 306–307

Cancer Chemotherapy and Pharmacology

Acute neurological toxicity of intrathecal cytosine arabinoside

A case report

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Summary. A patient developed severe neurological toxicity, with peripheral and cerebral components and hyponatraemia following one intrathecal injection of 80 mg cytosine arabinoside. The severity of his symptoms may reflect heavy prior neurotoxic chemotherapy.

Introduction

Since the advent of combined systemic and intrathecal chemotherapy many patients presenting with brain metastases from gestational trophoblastic or germ cell tumours have become long-term disease-free survivors [1, 6]. Patients with these tumours who are at risk of developing brain metastases also receive prophylactic intrathecal chemotherapy in some centres. The drug most frequently used for this purpose is methotrexate, but cytosine arabinoside (ARA-C) may be selected when there is a high risk of the tumour being resistant to methotrexate. We report a patient who developed severe neurological symptoms and signs after one dose of intrathecal ARA-C.

Case report

A 20-year-old man presented with haemoptysis and testicular swelling. Human chorionic gonadotrophin (HCG) was 100600 IU/l and alphafetoprotein (AFP) 38 ng/l at orchidectomy; a predominantly trophoblastic germ cell tumour was confirmed. He was also found to have a skin metastasis, multiple pulmonary metastases and a 3-cm para-aortic mass on ultrasound examination. Because of inappropriate affect a computed tomography (CT) scan of the brain was performed, which demonstrated two lesions, one in the right posterior parietal region and one in the left cerebral hemisphere. POMB/ACE chemotherapy was started (*cis*-platinum, vincristine, methotrexate and bleomycin alternating with actinomycin D, cyclophosphamide and etoposide), a 1-g/m^2 dose of methotrexate being used with folinic acid rescue [6]. He received six courses of POMB, after which vincristine, methotrexate and bleomycin alternated with ACE until serum HCG had been normal (< 5 IU/l) for 3 months. During the period in which the serum HCG was elevated he received intrathecal methotrexate 12.5 mg with each ACE course. The treatment and biochemical progress are shown in Fig. 1.

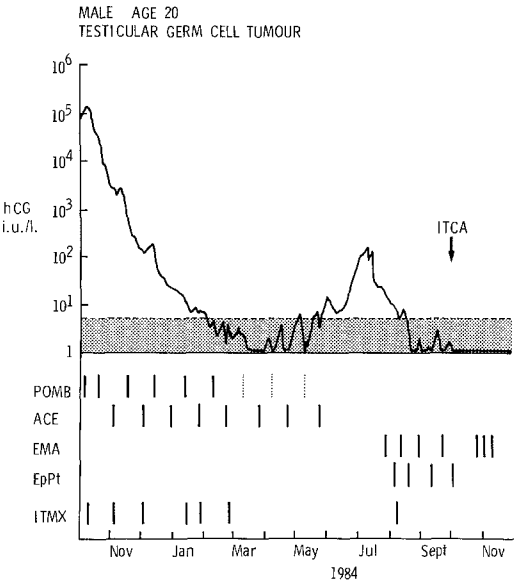

Fig. 1. Serum hCG and chemotherapy administered. *ITCA*, intrathecal cytosine arabinoside; *POMB*, *cis*-platinum, vincristine, methotrexate, bleomycin (*cis*-platinum omitted after 6th course); *ACE*, actinomycin D, cyclophosphamide, etoposide; *EMA*, etoposide, methotrexate, actinomycin D; *EpPt*, etoposide and *cis*-platinum; *ITMX*, intrathecal methotrexate. *Stippled area*, normal range for hCG

Immediately after treatment stopped the patient's serum β-HCg level rose to a peak of 137 IU/l. Although there had been almost complete resolution of brain CT scan abnormalities he still had several lesions > 2 cm in diameter on CT chest scan. A thoracotomy was performed at which all masses > 1 cm diameter were resected, and most contained active trophoblastic tumour. Chemotherapy was therefore restarted according to a regimen consisting of etoposide 200 mg/m^2 and *cis*-platinum 100 mg/m^2 (EpPt) as a 24-h infusion alternating every 8–10 days, depending on blood count and mucositis, with etoposide 100 mg/m^2 and actinomycin-D 0.5 mg on days 1 and 2 and methotrexate as a 100-mg/m^2 bolus followed by 200 mg/m^2 as a 12-h infusion on day 1 followed by folinic acid rescue (EMA). He received one intrathecal injection of methotrexate with the first EpPt course, but in view of the heavy pretreatment with methotrexate it was felt that any disease in the nervous system was likely to be resistant to this drug. He was

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therefore given 80 mg ARA-C intrathecally in preservative-free solution with the 4th course of EpPt and discharged home. At 48 h later he developed such pronounced muscle weakness that he could no longer climb stairs. He was admitted to his local hospital with retention of urine 4 days after the intrathecal injection. There he had an epileptic seizure. He was transferred to Charing Cross, where he had further seizures and was found to have neck stiffness and lower motor neurone weakness, which was worse in the legs than in the arms. There was evidence of upper motor neurone disease with bilateral extensor plantar responses. There was also diminished sensation in the lower limbs. His serum sodium was 128 mmol/l, calcium (adjusted for albumin) 2.12 mmol/l, magnesium 0.52 mmol/l. Lumbar puncture showed a CSF protein of 3.1 g/l. Microscopy showed red cells 794×10^9/l, polymorphs 1.6×10^9/l, lymphocytes 1.6×10^9/l. Culture was negative and no viruses were isolated. Over the next few days his condition deteriorated with profound anaesthesia, weakness, and dysarthria and further fits, which were controlled with phenytoin and by correcting the magnesium levels. Serum sodium, which fell to 107 mmol/l 3 days after admission, was corrected by fluid restriction and demeclocycline. The weakness progressed and respiratory function deteriorated, his vital capacity falling to 300 ml. He required mechanical ventilation for a short time following an epileptic seizure. After partial neurological recovery treatment continued with EMA only. He was finally discharged 8 weeks after the intrathecal ARA-C, still requiring a urinary catheter and with considerable motor and sensory loss in both legs. Slow neurological recovery has continued.

Discussion

Methotrexate has been associated with a necrotizing encephalopathy after prolonged periods of intrathecal therapy. Radiotherapy is believed to be a predisposing factor to this [3]. Arachnoiditis associated with neck stiffness and occasionally photophobia are the usual presenting symptoms. Paraplegia has been described following methotrexate therapy, and has been reported to recur after subsequent intrathecal instillation of ARA-C [7]. It is also known that administration of ARA-C by this route over a period of time is associated with occasional neurological effects and may be more frequent with radiotherapy [2, 5, 9]. Histological changes associated with this are mainly found in the white matter and peripheral myelin [5]. They differ from those associated with radionecrosis.

Systemic ARA-C given at a dose of 3 g/m^2 every 12 h for 12 doses has been associated with cerebellar degeneration with selective loss of Purkinje cells [8].

The neurological illness in the patient reported here was of acute onset and life-threatening in its intensity owing to production of the syndrome of inappropriate secretion of antidiuretic hormone and global muscle weakness. ARA-C is implicated both because of the close relationship in time between the intrathecal injection and the onset of the weakness and because of the well-established neurotoxicity of this compound. The fact that such profound neurotoxicity has not previously been reported after such a small dosage of ARA-C suggests that a number of other factors may also be implicated.

Although cerebral metastases were present at the time the patient's treatment started there was no evidence of their recurrence on CT scanning. However, the intensive prior intrathecal and systemic chemotherapy that he had received for his cerebral metastases may be contributory factors. Hypomagnesaemia, which was found in this patient, is associated with fits in patients receiving platinum [4], and this may well have been relevant here. The fact that this patient had received seven intrathecal injections of methotrexate together with systemic vincristine and *cis*-platinum, drugs which are known to be toxic to the peripheral nervous system, is probably the most important factor in this man's myelopathy, although a simple idiosyncratic reaction to the ARA-C cannot be completely discounted. Intrathecal ARA-C has been introduced without further problems [5] in at least one patient who had prevously developed neurotoxic symptoms following intrathecal thio-TEPA. Patients receiving the drug intrathecally in conjunction with other neurotoxic agents should be observed carefully with regard to neurological function.

It is important that all cases of neurological toxicity to ARA-C are reported to the regulatory authorities (as this case was) so that it can be determined whether pretreatment by certain drugs increases its incidence. Until this is clear methotrexate rather than ARA-C should remain the intrathecal drug of choice in the treatment of patients with cerebral metastases from germ cell tumours.

References

1. Athanassiou A, Begent RHJ, Newlands ES, Parker D, Rustin GJS, Bagshawe KD (1983) Central nervous system metastases of choriocarcinoma – 23 years experience at Charing Cross Hospital. Cancer 52: 1728
2. Brewer AC, Pitman SW, Dawson DM, Schoem WC (1977) Paraplegia following intrathecal cytosine arabinoside. Cancer 40: 2817
3. Goldberg ID, Bloomer WD, Dawson DM (1982) Nervous system toxic effects of cancer therapy. JAMA 247: 1437
4. Macauley VM, Begent RHJ, Phillips ME, Newlands ES (1983) Prophylaxis against hypomagnesaemia induced by *cis*-platinum combination chemotherapy. Cancer Chemother Pharmacol 9: 179
5. Mena H, Garcia JH, Velandia F (1981) Central and peripheral myelinopathy associated with systematic neoplasia and chemotherapy. Cancer 48: 1724
6. Newlands ES, Begent RHJ, Rustin GJS, Parker D, Bagshawe KD (1983) Further advances in the management of malignant teratomas of the testis and other sites. Lancet I: 948
7. Saiki JH, Thompson S, Smith S, Atkinson R (1972) Paraplegia following intrathecal chemotherapy. Cancer 29: 370
8. Winkelman MD, Hines JD (1983) Cerebral degeneration caused by high dose cytosine arabinoside. A clinicopathological study. Ann Neurol 14: 520
9. Wolff L, Zighelboim J, Gale RP (1979) Paraplegia following intrathecal cytosine arabinoside. Cancer 43: 83

Received March 4, 1985/Accepted September 3, 1985