Cancer Chemother Pharmacol (1991) 27: 329–330

034457049100014L

Cancer Chemotherapy and Pharmacology

Short communication

Acute reversible neurological deficit following intrathecal chemotherapy

H. Dunkelman[1, 3], H. M. Earl[1], and C. Twelves[1, 2]

[1] Department of Radiotherapy and Oncology, University College Hospital, London WC1E 6AU, UK
[2] Present address, Department of Medical Oncology, Guy's Hospital, London SE1 6RT, UK
[3] Present address, The Medical Centre, 45 Enderley Road, Harrow Weald HA3 5ER, UK

Received 31 May 1990/Accepted 29 August 1990

Summary. We report on two patients with non-Hodgkin's lymphoma (NHL) who developed reversible, short-lived neurological deficit following intrathecal (i.t.) chemotherapy. One patient received i.t. methotrexate for treatment of meningeal disease, and the other received i.t. methotrexate with cytosine arabinoside (ara-C) and hydrocortisone as central nervous system (CNS) prophylaxis. Although transient paresis following i.t. chemotherapy has previously been reported, it has been attributed to the preservatives contained in the diluents. Our two patients, however, received preservative-free solutions.

Introduction

Intrathecal (i.t.) methotrexate and ara-C are used in patients with lymphoma and leukaemia both for treatment of established central nervous system (CNS) disease and for CNS prophylaxis. In this paper we draw attention to a complication of i.t. treatment with preservative-free methotrexate and ara-C.

Case reports

Patient 1

A 43-year-old man presented with high, swinging fevers and multiple cranial nerve palsies, with no peripheral neurological deficit. Lymphoma cells were present in his cerebrospinal fluid (CSF) and the diagnosis of high-grade non-Hodgkin's lymphoma (NHL) was confirmed by liver biopsy. The patient was initially treated with i.t. methotrexate (12.5 mg), which was undiluted and contained no preservative. Five injections were given over a 6-week period, resulting in resolution of the cranial nerve signs. However, immediately after the sixth intrathecal injection through the L4–5 interspace, the patient developed complete paralysis of both legs and an ascending sensory loss to the T7 level. The neurological deficit progressed and was maximal at 20 min after i.t. injection. Over the following 30 min, the motor and sensory deficit resolved completely. The patient received no further i.t. treatment.

Patient 2

A 25-year-old woman presented with a large mediastinal mass that was diagnosed as a sclerosing B-cell mediastinal lymphoma [8, 11]. She was treated with systemic m-BACOD chemotherapy [13] and also received i.t. methotrexate, ara-C and hydrocortisone as CNS prophylaxis. Four courses of preservative-free i.t. therapy were given without incident. The fifth course of 12.5 mg methotrexate diluted in 5 ml 0.9% saline, 50 mg ara-C, and 30 mg hydrocortisone was injected through the L4–5 interspace. Immediately after the procedure, the patient developed complete paralysis and anaesthesia of the left leg. The spinal needle was re-introduced and CSF lavage was carried out over 1 h using 100 ml sterile, preservative-free physiological saline. During this time the neurological deficit resolved completely. No further i.t. treatment was given.

Discussion

Several factors have been thought responsible for transient or permanent neurological deficit following i.t. chemotherapy with methotrexate and ara-C. These include the nature of the diluent [12], contaminants introduced in the preparation of the drug [15], and the CSF fluid dynamics causing increased CSF drug concentration [3]. The most frequently implicated factor, however, is the presence of preservative in the methotrexate or ara-C preparation [7].

A review of the literature on paraplegia occurring after i.t. methotrexate or ara-C reveals that most patients who have developed immediate neurological problems after i.t. treatment had received preservative in the diluent [1,2, 4–6, 10, 12]. At that time, liquified methotrexate contained the preservatives methyl and propyl hydroxybenzoate, and methotrexate and ara-C were often diluted with water or physiological saline containing 0.9% (w/v) benzyl alcohol. Even in small quantities, these substances are toxic when given i.t. [9]. Experimentally in rats, benzyl alcohol has been shown to block the compound action potential in spinal roots, and longer exposure of the nerve

Offprint requests to: H. M. Earl

roots to these substances causes widespread demyelination and Wallerian degeneration [7].

Following the reports of this complication, i.t. chemotherapy has usually been given in preservative-free solutions. Our patients did not receive any preservative, and we therefore propose that the chemotherapeutic agents themselves were directly responsible for the neurological deficits. A high local concentration of methotrexate or ara-C may cause a temporary conduction block in the spinal roots or spinal cord, which resolves as the local concentration falls when the drug diffuses throughout the CSF volume. Another possible explanation is that acute reversible vascular spasm caused by the i.t. chemotherapy produces a transient neurological deficit as a result of ischaemia. Bleyer et al. [3] have also reported on five patients in whom neurotoxicity followed the i.t. administration of preservative-free methotrexate, and this was associated with CSF methotrexate levels higher than those observed in patients who developed no toxicity. However, the pattern of neurotoxicity in these patients was different from those reported herein and it progressed over several days.

The effect of additional i.t. chemotherapy following an episode of acute reversible neurological deficit is unknown, since neither of our patients received further treatment by that route. Ventriculolumbar perfusion has previously been reported for treating massive overdose of i.t. methotrexate [14]. It would be difficult to advocate this treatment in the event of the complication reported herein, but i.t. lavage with normal saline may be helpful in rapidly reducing the concentration of drug in the CSF.

References

1. Back EH (1969) Death after intrathecal methotrexate (letter) Lancet II: 1005
2. Bagshawe KD, Macgrath IT, Golding PR (1969) Intrathecal methotrexate (letter) Lancet II: 1258
3. Bleyer WA, Drake JC, Chabner BA (1973) Neurotoxicity and elevated cerebrospinal fluid methotrexate concentration in meningeal leukaemia. N Engl J Med 289: 770
4. Breuer AC, Pitman SW, Dawson DM, Schoene WC (1977) Paraparesis following intrathecal cytosine arabinoside. Cancer 40: 2817
5. Clark AW, Cohen SR, Nessenblatt MJ, Wilson SK (1982) Paraplegia following intrathecal chemotherapy. Neuropathologic findings and elevation of myelin basic protein. Cancer 50: 42
6. Gagliano RG, Costanzi JJ (1976) Paraplegia following intrathecal methotrexate. Cancer 37: 1663
7. Hahn AF, Feasby TE, Gilbert JJ (1983) Paraparesis following intrathecal chemotherapy. Neurology 33: 1032
8. Jacobson JO, Aisenberg AC, Lamarre L, Willett CG, Linggood RM, Miketic LM, Harris NL (1988) Mediastinal large cell lymphoma. An uncommon subset of adult lymphoma curable with combined modality therapy. Cancer 62: 1893
9. Nathan PW, Sears TA (1961) Action of methyl hydroxybenzoate on nervous conduction. Nature 192: 668
10. Nelson RW, Frank JT (1981) Intrathecal methotrexate-induced neurotoxicities. Am J Hosp Pharm 38: 65
11. Perrone T, Frizzera G, Rosai J (1986) Mediastinal diffuse large cell lymphoma with sclerosis. A clinicopathologic study of 60 cases. Am J Surg Pathol 10: 176
12. Saiki JH, Thompson S, Smith F, Atkinson R (1972) Paraplegia following intrathecal chemotherapy. Cancer 29: 370
13. Shipp MA, Yeap BY, Harrington DP, Klatt MM, Pinkus GS, Jochelson MS, Rosenthal DS, Skerm AT, Canellos GP (1990) The m-BACOD combination chemotherapy regimen in large cell lymphoma. Analysis of the completed trial and comparison with the m-BACOD regimen. J Clin Oncol 8: 84
14. Spiegel RJ, Cooper PR, Blum RH, Speyer JL, McBride D, Mangiardi J (1984) Treatment of massive intrathecal methotrexate overdose by ventriculolumbar perfusion. N Engl J Med 311: 386
15. Valerino DM (1972) Methotrexate impurities. Lancet II: 1025