*Anti-Cancer Drugs*, 1, pp. 33–35

# Severe polyneuropathy and motor loss after intrathecal thiotepa combination chemotherapy: description of two cases

**S Martín Algarra,[CA] I Henriquez, J Rebollo and J Artieda**

S Martín Algarra, I Henriquez and J Rebollo are at the Department of Oncology, and J Artieda is at the Department of Neurology, Clínica Universitaria de Navarra, Pamplona, Spain. Address reprint requests to Salvador Martín Algarra, MD, Department of Oncology, Clínica Universitaria de Navarra, P.O. Box 192, 31080-Pamplona, Spain.

**Two cases of severe delayed neurologic toxicity related to the administration of intrathecal (IT) combination chemotherapy including thiotepa (TSPA) are presented. Both cases developed axonal neuropathy with motor predominance in the lower extremities 1 and 6 months after IT chemotherapy was administered. Neurologic toxicities have been described with IT-methotrexate, IT-cytosine arabinoside and IT-TSPA. To our knowledge, however, axonal neuropathy following administration of these three agents has not been previously described. In spite of the fact that TSPA is a useful IT agent, its combination with MTX, ara-C and radiotherapy could cause severe neurotoxicity. This unexpected complication indicates the need for further toxicology research on IT-TSPA.**

*Key words:* Intrathecal thiotepa, axonal neuropathy.

## Introduction

Intrathecal (IT) chemotherapy is a customary treatment of leukemia, lymphoma, medulloblastoma, ependymoma and other primary or metastatic CNS tumors.[1,2] The common agents for IT chemotherapy are methotrexate (MTX) and cytosine arabinoside (ara-C), and neurotoxicity has been found related to the use of these agents whether alone or in combination, particularly with radiotherapy (Table 1).[3,4] IT-thiotepa (TSPA) has demonstrated activity in different meningeal and CNS neoplasms.[2,3] Phase I studies with this agent indicated that TSPA 10 mg/m$^2$ can be administered into the lumbar sac without serious toxicity.[5]

Nevertheless little is known regarding the use of IT-TSPA in combination with other agents. In this report, two cases of delayed severe neurologic toxicity related to the administration of IT combination chemotherapy, including TSPA, are presented.

## Case reports

### Case 1: (JMCR)

A 13-year-old boy diagnosed of medulloblastoma of cerebellum was referred, in December 1986, for radiotherapy and IT chemotherapy after radical surgery. At the time of admission the patient was healthy, alert, and oriented. Surgical scarring had healed. On physical examination no neurologic signs were found. Blood cell cerebrospinal fluid (CSF) studies were normal. CSF color was clear, and atypical cells were not found. Brain CT scan and myelography failed to demonstrate evidence of residual disease or spinal cord compression. IT chemotherapy consisting of TSPA 10 mg/m$^2$ daily for 2 days, ara-C 30 mg/m$^2$ daily for 3 days and MTX 6 mg/m$^2$ on day 1 was given. Treatment was repeated 10 days later. Craniospinal irradiation was begun immediately after the first cycle of chemotherapy up to a total dose of 30 Gy in 200 cGy fractions over 3 weeks. An additional boost of 20 Gy was subsequently delivered to the posterior CNS fossa. The total duration of radiotherapy was 5 weeks.

CT scan and myelography were respectively performed 8 and 11 weeks after IT chemotherapy and demonstrated no abnormal findings.

Two months later neurologic examination demonstrated a decrease in deep tendon reflexes. CT scan and myelography performed at that time were considered normal.

Six months after IT chemotherapy, the patient complained of weakness and paresthesia in the lower extremities. Neurologic examination revealed dropping of the left foot, with 'steppage' walking and complete absence of deep tendon reflexes. CT scan, magnetic resonance imaging (MRI), and myelography did not show any evidence of local relapse or spinal cord compression. CSF cytology, protein contents, glucose, and electrolytes were found normal as well.

Motor and sensory nerve conduction studies with electromyography suggested axonal neuropathy with motor predominance, more evident in the left lower extremity. A month later deep tendon reflexes were totally abolished. Babinski's reflex was normal, as it was epicritic, protopathic, and pain sensitive. Sural nerve biopsy was performed which indicated axonal neuropathy with secondary demyelination and evidence of neural regeneration. Two years after treatment the patient continued in complete remission and maintained the neurologic deficits unchanged.

### Case 2: (MAC)

A 20-year-old male diagnosed of medulloblastoma of cerebellum was admitted in our center to receive IT chemotherapy following radical surgery and craniospinal irradiation up to a dose of 55 Gy, 35 Gy on holocranial and spinal fields, and a boost of 20 Gy over the posterior fossa, given over 7 weeks. At the time of admission the patient was asymptomatic. Physical examination and laboratory values including CSF were normal.

IT chemotherapy with TSPA 8 mg/m$^2$ on day 3, ara-C 25 mg/m$^2$ on days 1–3, and MTX 6 mg/m$^2$ on day 1 was given. Two further IT chemotherapy treatments were subsequently given with the same doses and scheduled for 2 and 4 months later. IT dexamethasone 6 mg on days 1–3 was administered in each treatment.

One month after the last IT treatment the patient developed incontinence, weakness, wasting, and paresthesia in the lower extremities and perineum. Neurologically the patient was awake, fully alert and oriented. Cranial nerves were grossly intact. There was a loss of muscular strength with balances ranging from 3/5 to 4/5 in the different areas. Deep tendon reflexes were abolished. No sensitivity disturbances were found. Motor and sensitive nerve conduction studies and electromyography showed a diminution of motor trunk conduction velocity of the lower extremities with diminution of evoked response muscle amplitude and nerve sensory potential. Electromyography registered spontaneous activity during complete muscle relaxation in all lower extremity muscles as well as the loss of the motor unit potentials during nervous stimuli, particularly in the distal muscles. These studies suggested axonal neuropathy with the lower extremities motor predominant. Magnetic resonance imaging (MRI) and myelography indicated no evidence of relapse, or subarachnoid metastases, and no intramedullary abnormality or intradural drop metastases. The conus medullaris was normal.

At the time of this report the patient is tumor-free and has been off therapy for 14 months. He is undergoing physical rehabilitation and using orthopedic shoes. Neurologic status remain unchanged.

## Discussion

TSPA is a polyfunctional alkylating drug used in antineoplastic therapy for 35 years.[6] Preclinical and phase I clinical studies of IT-TSPA were carried out by Weiss in 1974.[7] Since then several authors have used this approach with negligible toxicity.[5,8–10] Nevertheless, Gutin *et al.* found severe and progressive neurologic defects following IT administration of TSPA in 2 out of 10 patients with malignant meningeal disease.[11] The two cases described in this report developed neurotoxicity with weakness and paresthesia in the lower extremities a few weeks or months following IT chemotherapy. Neurologic examination, motor and sensory nerve conductive studies and electromyogram have demonstrated an axonal polyneuropathy of motor predominance. Nerve biopsy performed in the first case indicated axonal neuropathy with secondary demyelination.

Neurologic toxic syndromes previously described with IT-MTX, IT-ara-C or after its combination with radiotherapy[3] (Table 1), are different from the neurotoxicity observed in the two patients this report. Gutin *et al.* first observed a similar neurotoxic complication after IT-TSPA 10 mg/m$^2$ administered on alternate days for four times and two weekly consolidation doses.[12] The acute and progressive appearance of symptoms in their patients could have been related to the cumulative high doses of TSPA administered. The dose of TSPA and the frequency of administration of IT chemotherapy in our two patients have been lower than the maximal tolerated dose delivered by Weiss *et al.*[7] and Gutin *et al.*[11]

**Table 1.** Neurological side effects of IT with MTX, ara-C, and TSPA

| | MTX | ara-C | TSPA |
|---|---|---|---|
| Acute | Meningeal irritation<br>Arachnoiditis | Paraplegia<br>Reversible paralysis[b] | Paraplegia<br>Paresthesia[b] |
| Subacute | | Paraplegia | Radiculoneuropathy[c] |
| Chronic | Encephalopathy[a]<br>Somnolence[a] | Leukoencephalopathy[a]<br>Cerebral atrophy[a] | Cerebral atrophy[a] |

[a] Mainly with simultaneous radiotherapy.
[b] During infusion of IT chemotherapy.
[c] Observed with MTX, ara-C, and radiotherapy in both patients.

In a previous work these authors related neurologic changes observed after IT-TSPA to chemical arachnoiditis induced by the nonphysiologic ionic content of the solution.[5] However, symptoms induced by chemical toxicity are characterized by acute arachnoiditis, usually mild and transient, and no prospective clinical comparison has ever proven that one diluent was safer than another.[12]

Since lower doses of IT-TSPA have been used without serious complications, the unusual neurologic findings observed in these patients might be satisfactorily explained as due to the synergism of MTX, ara-C and/or radiotherapy. Our data suggest that despite TSPA being a useful IT agent, its combination with MTX, ara-C and radiotherapy might cause severe neurotoxicity.

This unexpected complication indicates the need of further toxicology research on IT-TSPA.

**Acknowledgments**—The authors wish to acknowledge Drs I de Castro and MT Inaraja for their helpful discussions, and Miss MA Andueza for the skilful preparation of the manuscript.

## References

1. Bleyer WA. Current status of intrathecal chemotherapy for human meningeal neoplasms. *Nat Cancer Inst Monogr* 1977; **46**: 171–178.
2. Friedman HS, Colvin OM, Ludeman SM, Schold LC, Boyd VL. Experimental chemotherapy of human medulloblastoma with classical alkylators. *Cancer Res* 1986; **46**: 2827–2833.
3. Kaplan SR, Wiernik PH. Neurotoxicity of antineoplastic drugs. *Sem Oncol* 1982; **9**: 103–130.
4. Saleh MN, Christian ES, Diamond BD. Intrathecal cytosine arabinoside induced acute, rapidly reversible paralysis. *Am J Med* 1989; **86**: 729–730.
5. Gutin PH, Weiss HD, Wiernik PH, Walker MD. Intrathecal *N,N′,N″*-triethylenethiophosphoramide [THIOTEPA (NSC 6396)] in the treatment of malignant meningeal disease: phase I-II study. *Cancer* 1976; **38**: 1471–1475.
6. American Hospital Formulary Service. *Drug Information 88*. McEvoy GK ed. Bethesda, MD: American Society of Hospital Pharmacists, 1988; 55–56.
7. Weiss HD, Walker MD, Wiernik PH, Dalgard D. Preclinical and phase-I clinical studies of intrathecal *N,N′,N″*-triethylenephosphoramide (THIOTEPA-NSC 6396). *Proc Am Assoc Cancer Res* 1974; **15**: 65 (abstract).
8. Strong JM, Collins JM, Lester C, Poplack DG. Pharmacokinetics of intraventricular and intravenous *N,N′,N″*-triethylenethiophosphoramide (Thiotepa) in Rhesus monkeys and humans. *Cancer Res* 1986; **46**: 6101–6104.
9. Trump DL, Grossman SA, Thompson G, Murray K, Wharam M. Treatment of neoplastic meningitis with intraventricular Thiotepa and Methotrexate. *Cancer Treat Rep* 1982; **66**: 1549–1551.
10. Giannone L, Greco FA, Hainsworth D. Combination intraventricular chemotherapy for meningeal neoplasia. *J Clin Oncol* 1986; **4**: 68–73.
11. Gutin PH, Levi JA, Wiernik PH, Walker MD. Treatment of malignant disease with intrathecal thiotepa: a phase II study. *Cancer Treat Rep* 1977; **61(5)**: 885–7.
12. Green L. Therapy consultation. *Clin Pharm* 1988; **7**: 265–6.

*(Received 5 July 1990; accepted 16 August 1990)*