Published in final edited form as:

J Neurooncol. 2015 April ; 122(2): 391–398. doi:10.1007/s11060-015-1727-z.

Myelopathy following intrathecal chemotherapy in adults: a single institution experience

David Cachia, MD MRCP(UK)*,

The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, 1515 Holcombe Blvd, Houston, TX 77030, Phone: 713-792-1263 Fax: 7137944999
dcachia@mdanderson.org

Carlos Kamiya-Matsuoka, MD*,

MD Anderson Cancer Center, Dept. of Neuro-Oncology

Chelsea C Pinnix, MD,

MD Anderson Cancer Center, Dept. of Radiation Oncology

Linda Chi, MD,

MD Anderson Cancer Center, Dept. of Diagnostic Radiology

Hagop M Kantarjian, MD,

MD Anderson Cancer Center, Dept. of Leukemia

Jorge E Cortes, MD,

MD Anderson Cancer Center, Dept. of Leukemia

Naval Daver, MD, and**

MD Anderson Cancer Center, Dept. of Leukemia

Karin Woodman, MD**

MD Anderson Cancer Center, Dept. of Neuro-Oncology

Abstract

Methotrexate and cytarabine arabinoside are frequently administered intrathecally in the prophylaxis and treatment of patients with hematological malignancies. Myelopathy as a complication of intrathecal chemotherapy is rare in adults, with most of the cases described in the literature occurring in the pediatric population. Between January 2010 and March 2014, 587 newly diagnosed B-cell acute lymphoblastic leukemia and 24 chronic myeloid leukemia lymphoid blast phase patients were seen at The University of Texas MD Anderson Cancer Center. This case series discusses 7 adult cases deemed to have intrathecal chemotherapy-induced myelopathy between 2010–2014 at MD Anderson Cancer Center. Five out of the 7 patients had T2 abnormalities involving the dorsal columns of the spinal cord. An elevated myelin basic protein level was noted in the 2 patients in whom it was checked. The wide range of dosage and timing

Correspondence to: David Cachia.

*Dr Cachia and Dr Kamiya-Matsuoka contributed equally to the preparation of this manuscript

**Dr Daver and Dr Woodman are co-corresponding authors

Conflict of interest disclosure: Authors report no conflict of interest

with respect to intrathecal chemotherapy administration suggests an idiosyncratic reaction or individual threshold to the development of myelopathy. By describing the largest case series of myelopathy in adults, we aim to raise awareness about this rare albeit devastating complication. Based on the 7 cases described we would recommend – MRI of the spine with T2-weighted imaging in the sagittal and axial planes in leukemia patients with unexplained myelopathy and consideration to delay intrathecal chemotherapy until after an extensive work-up to rule out CNS leukemia. Though more data are needed on the use of folate metabolites, preliminary results have shown some promise in the treatment of methotrexate-induced myelopathy and may be a potential consideration for future patients suspected to have chemotherapy induced myelopathy.

Keywords

intrathecal chemotherapy; myelopathy; lymphoid leukemia; spinal cord dorsal columns T2 hyperintensity

Introduction

Intrathecal (IT) chemotherapy in combination with systemic chemotherapy is an effective treatment modality used in the prophylaxis and treatment of central nervous system (CNS) disease in patients with hematological malignancies. IT agents commonly used in various chemotherapeutic regimens include methotrexate (MTX) and cytarabine arabinoside (Ara-C). Neurological side effects from IT chemotherapy vary from mild asymptomatic forms of arachnoiditis diagnosed on MRI to leukoencephalopathy and myelopathy [1, 2]. The more severe neurological complications have been reported more frequently in the pediatric literature. [3] The aim of this paper is to describe rare but debilitating neurological complications that may occur as sequelae of IT chemotherapy. Herein, we describe the clinical manifestations, radiological features and clinical outcomes in 7 adult patients with lymphoid leukemia who developed myelopathy following IT chemotherapy.

Methods

Patients

Between January 2010 and March 2014, 587 newly diagnosed B-cell acute lymphoblastic leukemia (ALL) and 24 chronic myeloid leukemia (CML) lymphoid blast phase patients were seen at The University of Texas MD Anderson Cancer Center (MDACC). The 2 most frequently used induction-consolidation regimens at MDACC include the HyperCVAD regimen and the Augmented Berlin-Frankfurt-Münster (BFM) therapy [4, 5]. CNS prophylaxis in the hyper-CVAD regimen comprised alternating intrathecal therapy with methotrexate and cytarabine on days 2 and 7 of each hyperCVAD course for a total of 8 or 12 doses, depending on the risk of CNS relapse [6]. The augmented BFM patients were differentiated into early responder group (<5% marrow blasts on cycle 1 day 15) and late responder group (>5% marrow blasts on cycle 1 day 15). Early responders received 12 intrathecal therapies, whereas slow responders received 16 treatments comprised of alternating cytarabine and methotrexate. The first dose of intrathecal cytarabine was administered on cycle 1 day 1 [5].

During this timeframe, a total of 7 adult patients with acute lymphoblastic leukemia (ALL), Burkitt's lymphoma/leukemia or chronic myeloid leukemia (CML) in lymphoid blast crisis who received IT chemotherapy for the prophylaxis or treatment of CNS disease were evaluated by the neurology consult service at MDACC for clinical signs and symptoms suggestive of myelopathy. These 7 patients were retrospectively reviewed. The clinical features, laboratory data, electromyographic (EMG) and MRI findings in these seven patients are described herein. This retrospective study was approved by the ethics committee of MDACC.

Results

The systemic disease status, frequency and dose of IT chemotherapy, time to onset of symptoms, and clinical characteristics of the 7 patients are listed in Table 1. There were four men and three women, with a median age of 48 (range, 18–70 years). Five of the seven patients were being treated for B-cell ALL, one for Burkitt's leukemia/lymphoma, and one for CML-lymphoid blast crises. All patients received both IT Ara-C and MTX for the prophylaxis or treatment of CNS disease.

We reviewed the radiographic findings in the 611 patients treated at MDACC. 489 patients (470 ALL + 19 CML patients) (81%) did not have a spine MRI, 91 patients (86 ALL and 5 CML patients) had an MRI spine which did not show any spinal cord abnormality (15%), 14 patients (all ALL patients) had evidence of enhancement suggestive of LMD (0.02%), 13 patients (all ALL patients) had evidence of leukemic infiltration (0.02%) and 5 patients (4 ALL patients and 1 CML patient) had preferential non-enhancing T2 hyperintensity involving the dorsal columns (<0.01%).

All seven patients who developed a myelopathy, had spinal cord abnormalities seen on MRI with 5 of the 7 patients manifesting T2 abnormalities involving the dorsal columns of the spinal cord as shown in Fig. 1 (MRI from patient #4). In the remaining 2 cases, enhancement along the conus medullaris and cauda equina nerve roots was noted and was initially thought to represent leptomeningeal disease, but the CSF was repeatedly negative.

The time to onset of neurological symptoms was variable, ranging from 2 days to 7 months from the initiation of IT chemotherapy. The time to maximal neurological deficit from onset of symptoms ranged from 10 days to 1 month (median = 14 days). Median survival was 3.1 months from the onset of myelopathy. Table 2 summarizes the investigations done on these 7 patients. Cerebrospinal fluid (CSF) analysis revealed elevated protein at presentation in 5 patients, decreased glucose in 0 patients and greater than 5 white blood cells (WBC) in CSF in 1 patient. All 7 patients eventually developed elevated protein levels in the CSF during the course of the myelopathy. CSF myelin basic protein (MBP), a marker of CNS inflammation and trauma, was assessed in 2 patients and was significantly elevated in both. Cytological evaluation of the CSF was repeatedly normal in all 7 patients (patients had CSF sent for cytology between 3–13 times per patient) whilst CSF flow cytometry was performed in 4 out of the 7 cases and was also negative. Despite normal cytology, the high clinical suspicion that the neurological symptoms were secondary to CNS leukemia prompted continuation of IT-chemotherapy for at least 1 more cycle beyond the onset of myelopathy

symptoms in 5 of 7 patients. Lower extremity weakness of varying degrees was noted in all patients with 5 of 7 patients progressing to paraparesis. Two patients temporarily improved after discontinuation of IT chemotherapy (patient 1 and 7) but subsequently deteriorated with multi-organ failure (patient 1) and leptomeningeal disease (patient 7). The treatments for these 7 patients varied from the use of high dose steroids to intravenous immunoglobulin to radiation therapy with no difference in the outcome (Table 1). Patient #5 was the only patient to have an autopsy. The autopsy revealed almost complete transverse necrosis at the upper thoracic level, with small remnants of central gray matter showing ischemic ("red neuron") changes. The lower thoracic cord also showed necrosis, with slightly greater preservation of the central gray matter and ischemic change similar to those seen in the upper thoracic cord. The cervical cord showed degeneration of the posterior columns, consistent with a Wallerian-like degeneration. The lumbar and sacral cord sections showed patchy edematous vacuolation and degeneration of the white matter columns. These histopathologic findings correlate accurately with the anatomic distribution of spinal cord abnormalities seen on antemortem MRI.

Discussion

The etiology of non-leukemic myelopathy in patients receiving intrathecal chemotherapy remains unclear. The neurotoxicity may be a result of aseptic meningitis incited by the preservative used in the diluent or alternatively in the case of methotrexate, it may be a result of local depletion of folate secondary to methotrexate. However, similar neurologic complications have been reported in patients who were given intrathecal preservative-free methotrexate or in those receiving Ara-C, suggesting that alternate mechanisms may be involved. [7]

Methotrexate is known to inhibit the enzyme dihydrofolate reductase which catalyzes the conversion of dihydrofolate (DHF) to tetrahydrofolate (THF) [8]. In the biologically active form, 5-methyl-THF is a donor of the methyl group for producing methionine and, in turn, S-adenosylmethionine (SAM). Therefore, IT methotrexate treatment can induce demyelination, by a pathogenic process similar to subacute combined degeneration (SACD), i.e. deficiency of methionine and SAM. The development of neurotoxic effects with IT-chemotherapy has been correlated with a high CSF level of methotrexate. [9] However, in our patients symptoms developed not only in patients who had received multiple doses of IT MTX, but also among those who had received one dose of IT chemotherapy. Also, myelopathy developed over a variable time range, from 2 days to up to 7 months after initiation of IT chemotherapy. In the pediatric literature a similar wide range has been reported. [10] These findings suggest that the toxic effects of methotrexate do not seem to be dose-related but may be related to individual sensitivity.

Why these 7 cases occurred in a single institution over a short period of time is unknown. We discussed these cases with other cancer institutions where the occurrence of this relatively rare complication of IT chemotherapy has not changed and no recent spikes in incidence of myelopathy have been observed. A few potential reasons for the unexpectedly high frequency of these cases in our institution include:

1. the high volume of B-cell ALL patients seen at MDACC (from January 2010 to March 2014 we had a total of 574 newly diagnosed B-cell ALL and 28 CML-lymphoid blast phase patients),
2. the increased survival of B-cell ALL patients [11–13] and
3. the increased awareness and attention to this phenomenon in our institution.

In our patients, we have no proof that MTX was the cause of the progressive myelopathy especially since all of the patients also received IT cytarabine. Liposomal cytarabine has been described in the literature as causing myelopathy as a complication of treatment in 2.5% of cases [14]. However in our case series, given the radiographic findings of preferential posterior column involvement, and knowing the biochemical similarities between methotrexate and vitamin B12 deficiency induced SCD, we believe that methotrexate was the more likely potential cause of neurological symptoms.

MRI is the most sensitive radiologic technique in the diagnosis of myelopathy. MRI abnormalities in patients receiving IT chemotherapy are non-specific and include cord swelling, T2 hyperintensity, and contrast enhancement. Five of 7 patients demonstrated longitudinal hyperintensities involving mostly the dorsal columns and to a varying degrees the lateral corticospinal tracts. This pattern has been described in other small case series and case reports. However a normal spine MRI does not exclude myelopathy [15]. This demonstrates that to make a diagnosis of IT induced myelopathy, a high index of suspicion is required in the appropriate clinical setting. In the remaining 2 of 7 cases, enhancement along the conus medullaris and cauda equina nerve roots was present.

EMG studies were performed on 5 out of the 7 patients. In 3 of the 5 patients, there was evidence of a severe polyneuropathy or polyradiculoneuropathy on EMG. In the two patients who did not have evidence of severe polyradiculoneuropathy (patients 5 and 7) one possible reason these severe changes were not seen could be the fact that the EMG was done relatively early in the course of the clinical spectrum (at 10 weeks and 2 weeks from the onset of weakness). This neurophysiological worsening over time was also reflected in the elevation of CSF protein in the same patients: 1, 2, 5 and 7 (patient 6 had only 1 spinal tap), indicating a correlation between the two studies and suggesting a possible measure to monitor treatment efficacy. Although EMG does not allow the clear distinction between a peripheral process and a central cause of weakness early on during the course of the disease, discordance on needle EMG showing mild denervation changes but a total absence of motor units (as seen in patient 6) should alert the treating physician to the possibility of a central cause. Early on, acute denervation changes such as fibrillation potentials and positive sharp waves are non-specific and do not allow localization.

One of the concerning questions in these patients is the ability to successfully distinguish between leukemic infiltration of the spinal cord and neurotoxic spinal cord damage since the treatment is drastically different for the two scenarios. This is especially difficult to determine when there is an elevated protein level in the CSF such as occurred in 5 of the 7 patients at presentation. In fact in 5 of 7 patients, IT chemotherapy was continued for at least 1 cycle after the onset of neurological symptoms due to the concern that the neurological symptoms were secondary to leukemic infiltration. This diagnostic uncertainty is

underscored by the fact that the sensitivity of CSF cytopathological analysis to detect tumor cells is only 70% after the first lumbar puncture, approaching 90% and 95% if the puncture is repeated two or three times, respectively [16]. There is some evidence that elevated levels of MBP in the CSF could reflect spinal cord damage rather than leukemic infiltration since MBP is a protein produced by oligodendrocytes and is the major constituent of the myelin sheath of axons. [17] Though this was checked in only 2 of our cases, the levels of MBP were significantly elevated in both patients. Other causes of elevated CSF protein include Guillain Barre, and infectious processes which were excluded in all 7 patients by EMG and CSF analysis, respectively. CSF flow obstruction leading to pooling of intrathecal methotrexate is another cause that can be investigated by performing CSF flow studies prior to the administration of intrathecal medications. However CSF flow studies are not routinely done in most institutions and are not well standardized. Unfortunately none of our patients had this test done, although the likelihood that CSF flow obstruction was a principal cause of myelopathy in our cluster of cases is very low.

Treatment with high dose folate metabolites has shown some promising results in patients with methotrexate induced myelopathy and may be a potential consideration for future patients suspected to have chemotherapy induced myelopathy. [18]. Drachtman et al reported that dextromethorphan was effective in treating subacute methotrexate toxicity in children [19]. Interestingly the 2 patients in our series that received dextromethorphan improved temporarily. However, they also received other concurrent treatments, making it difficult to draw a direct conclusion. Further research is required to establish an effective and definite diagnostic and treatment approach for these patients.

Acknowledgements

Mrs Sherry A Pierce for her help with data collection.

References

1. McLean DR, Clink HM, Ernst P, Coates R, al Kawi MZ, Bohlega S, Omer S. Myelopathy after intrathecal chemotherapy. A case report with unique magnetic resonance imaging changes. *Cancer*. 1994; 73:3037–3040. [PubMed: 8200001]
2. Skullerud K, Halvorsen K. Encephalomyelopathy following intrathecal methotrexate treatment in a child with acute leukemia. *Cancer*. 1978; 42:1211–1215. [PubMed: 581272]
3. Bay A, Oner AF, Etlik O, Yilmaz C, Caksen H. Myelopathy due to intrathecal chemotherapy: report of six cases. *J Pediatr Hematol Oncol*. 2005; 27:270–272. [PubMed: 15891563]
4. Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M, Pierce S, Huh Y, Andreeff M, Koller C, Ha CS, Keating MJ, Murphy S, Freireich EJ. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol*. 2000; 18:547–561. [PubMed: 10653870]
5. Rytting ME, Thomas DA, O'Brien SM, Ravandi-Kashani F, Jabbour EJ, Franklin AR, Kadia TM, Pemmaraju N, Daver NG, Ferrajoli A, Garcia-Manero G, Konopleva MY, Cortes JE, Borthakur G, Garris R, Cardenas-Turanzas M, Schroeder K, Jorgensen JL, Kornblau SM, Kantarjian HM. Augmented Berlin-Frankfurt-Munster therapy in adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL). *Cancer*. 2014
6. Cortes J, O'Brien SM, Pierce S, Keating MJ, Freireich EJ, Kantarjian HM. The value of high-dose systemic chemotherapy and intrathecal therapy for central nervous system prophylaxis in different risk groups of adult acute lymphoblastic leukemia. *Blood*. 1995; 86:2091–2097. [PubMed: 7662956]

7. Wolff L, Zigelboim J, Gale RP. Paraplegia following intrathecal cytosine arabinoside. *Cancer*. 1979; 43:83–85. [PubMed: 282937]
8. Chabner, BA.; Longo, DL. *Cancer chemotherapy and biotherapy: principles and practice*. Lippincott Williams & Wilkins; 2011.
9. Watterson J, Toogood I, Nieder M, Morse M, Friedrich S, Lee Y, Moertel CL, Priest JR. Excessive spinal cord toxicity from intensive central nervous system-directed therapies. *Cancer*. 1994; 74:3034–3041. [PubMed: 7954266]
10. Dunton SF, Nitschke R, Spruce WE, Bodensteiner J, Krous HF. Progressive ascending paralysis following administration of intrathecal and intravenous cytosine arabinoside. A Pediatric Oncology Group study. *Cancer*. 1986; 57:1083–1088. [PubMed: 3455842]
11. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, Trama A, Visser O, Brenner H, Ardanaz E, Bielska-Lasota M, Engholm G, Nennecke A, Siesling S, Berrino F, Capocaccia R. Cancer survival in Europe 1999–2007 by country and age: results of EUROCare--5-a population-based study. *Lancet Oncol*. 2014; 15:23–34. [PubMed: 24314615]
12. Pulte D, Gondas A, Brenner H. Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. *Blood*. 2009; 113:1408–1411. [PubMed: 18974371]
13. Pulte D, Redaniel MT, Jansen L, Brenner H, Jeffreys M. Recent trends in survival of adult patients with acute leukemia: overall improvements, but persistent and partly increasing disparity in survival of patients from minority groups. *Haematologica*. 2013; 98:222–229. [PubMed: 22929974]
14. Chamberlain MC. Neurotoxicity of intra-CSF liposomal cytarabine (DepoCyt) administered for the treatment of leptomeningeal metastases: a retrospective case series. *J Neurooncol*. 2012; 109:143–148. [PubMed: 22539243]
15. Teh HS, Fadilah SA, Leong CF. Transverse myelopathy following intrathecal administration of chemotherapy. *Singapore Med J*. 2007; 48:e46–e49. [PubMed: 17304378]
16. Glantz MJ, Cole BF, Glantz LK, Cobb J, Mills P, Lekos A, Walters BC, Recht LD. Cerebrospinal fluid cytology in patients with cancer: minimizing false-negative results. *Cancer*. 1998; 82:733–739. [PubMed: 9477107]
17. Pouw MH, Hosman AJF, van Middendorp JJ, Verbeek MM, Vos PE, van de Meent H. Biomarkers in spinal cord injury. *Spinal Cord*. 2009; 47:519–525. [PubMed: 19153591]
18. Ackermann R, Semmler A, Maurer GD, Hattingen E, Fornoff F, Steinbach JP, Linnebank M. Methotrexate-induced myelopathy responsive to substitution of multiple folate metabolites. *J Neurooncol*. 2010; 97:425–427. [PubMed: 19821069]
19. Drachtman RA, Cole PD, Golden CB, James SJ, Melnyk S, Aisner J, Kamen BA. Dextromethorphan is effective in the treatment of subacute methotrexate neurotoxicity. *Pediatr Hematol Oncol*. 2002; 19:319–327. [PubMed: 12078863]

Fig. 1.

Prototypic MRI spine findings on T2 –weighted imaging in Patient 4. T2 sagittal with fat saturation (A). T1 sagittal post contrast (B). T2 axial at C1-vertebra level (C) and T2 axial at T1-vertebra level (D). MRI findings may be normal in patients with IT-related myelopathy. When the MRI is abnormal, T2 hyperintensity preferentially involving the dorsal columns (A, C, and D) without enhancement (B) is typically seen, and at times symmetrical involvement of other tracts, including the lateral columns (arrow) (D).

Table 1

Demographics, clinical course and outcomes of patients described in this study

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age	70	59	18	32	48	50	35
Diagnosis	B-ALL Ph ⁻	B-ALL Ph ⁻	Burkitt's Lymphoma	B-ALL Ph ⁻	B-ALL	CML blast phase Ph ⁺	B-ALL Ph ⁻
Disease Status	Newly diagnosed	Newly diagnosed	CNS relapse	CNS relapse	Relapse	CNS relapse	CNS relapse
BM status at onset of neurological symptoms	No evidence of leukemia	Hypoplastic marrow post-chemotherapy	No evidence of leukemia	Persistent lymphoblastic leukemia	Hypoplastic marrow post-chemotherapy	No evidence of leukemia	No evidence of acute leukemia
Prior systemic Rx*	11/1/11–12/19/13 Hyper-CVAD+ rituximab + inotuzumab ozogamycin	6/8/13 Hyper-CVAD+ Ofatumumab	5/13 4 cycles of R-hyper-CVAD (augmented regime started in cycle 3) 9/12/13–10/2/13 Humanized Fc-engineered anti CD19 Ab: MOR0028	7/25/12 HperCVAD 9/18/12 Augmented BFM till consolidation cycle 2 5/15/13 hyper-CVAD + evrolimus x2 cycles 7/19/13 clofarabine, idarubicin, cytarabine, rituximab, vincristine 8/28/13 Humanized Fc-engineered anti CD19 Ab. x2 cycles: MOR0028 12/2/13 MOAD regimen	8/17/12–2/21/13 CALGB 10403 ALL regimen 3/7/13 SAR3419 (CD19 Ab-Maytansine conjugate) x3 doses 3/29/13–7/14/13 Hyper-CVAD+ inotuzumab ozogamycin	12/10–3/10 Imatinib 9/11 Allogenic peripheral blood stem cell transplant with conditioning consisting of cyclophosphamide	6/10 Hyper-CVAD x 5 cycles + POMP maintenance till 2/13 8/16/13 Augmented hyperCVAD
CNS-directed radiation Rx prior to myelopathy onset	None	None	None	None	None	None	7/12/12–7/24/13 WBRT
Date range of current IT therapies (From-To)	11/4/13 (MTX)	6/10/13 (MTX) 6/14/13 (ARA-C)	9/4/13 to 11/20/2013	5/16/13 to 12/30/13	3/19/13 (ARA-C) 4/1/13 (MTX)	5/13–7/13	7/13–9/13
IT total dose on current IT regimen	1 MTX= 12mg	1 MTX= 12mg 1 ARA-C =100mg	6 MTX= 72mg 6 ARA-C= 480mg	11 MTX= 66mg 15 ARA-C=1500mg	1 MTX=12mg 1 ARA-C= 100mg	N/A*	2 MTX= 12mg 4 ARA-C=400mg
Prior IT chemo	No	No	Yes (5/13–6/13)	No	Yes (12/12–1/13)	No	Yes(6/10)
Time to neurological signs/symptoms after IT 1 st dose (current regimen)	2 days after MTX	5 days after MTX	2 months	7 months	1 week after MTX	2 months	2 months
Time to maximal deficit	10 days	1 months	14 days	1 month	14 days	14 days	1 month
Neurological Signs & Symptoms	Back pain, urinary/fecal incontinence, Paraplegia, LE areflexia, saddle	Urinary/fecal incontinence, Saddle anaesthesia, T6 sensory level, paraplegia, LE	T8 sensory level, paraplegia, LE areflexia, bilateral positive Babinski's,	Saddle anaesthesia, paraplegia, urinary/fecal incontinence, LE areflexia, bil positive	Saddle anaesthesia, T8 sensory level, LE paraplegia, urinary/fecal incontinence,,	Urinary/fecal incontinence, paraplegia, T5 sensory level, absent LE reflexes,	Urinary/fecal incontinence, saddle anaesthesia, Paraparesis, bilateral positive Babinski's,

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
	anaesthesia, absent Babinski's	areflexia, absent Babinski's		Babinski's	absent LE reflexes, absent Babinski's	Plantars mute bil.	2+ KJ, absent AJ, Numbness to knees bil.
Treatment received	Dexamethasone, dextromethorphan, IVIG 5 days	Dexamethasone, IVIG $\times$ 5 days, Vitamin B12	Dexamethasone, Vit B12, IVIG $\times$ 5 days	Dexamethasone, folic acid, CSRT	IVIG $\times$ 5 days	CSRT	Pregabalin, dextromethorphan
Outcome	Neurological improvement but died 1 month after onset of symptoms from MOF	No neurological improvement. Alive at 6 months post onset neuro symptoms	No neurological improvement. Died 5 weeks after onset from MOF	No neurological improvement. Died 5 months post onset neuro symptoms	No neurological improvement. Died 2 months post onset neuro symptoms	No neurological improvement 6 months post onset. Died 7 months post onset of neuro symptoms	Neurological improvement post rehab (wheelchair $\rightarrow$ walker) but developed LMD 2 months later with neurological deterioration

* HyperCVAD and augmented BFM (in combination with monoclonal antibodies) are the most commonly used regimens for patients with B-ALL at MDACC. For details of HyperCVAD and augmented BFM regimens please see the text page 3.

* Patient received both IT methotrexate and Ara-C at OSH but doses are not known

Abbreviations: AJ: ankle joints, B-ALL: B- cell acute lymphocytic leukemia, BM: bone marrow, CSRT: craniospinal radiation therapy, IVIG: intravenous immunoglobulin, KJ: knee joints, LE: lower extremities, LMD: leptomeningeal disease, MDACC: MD Anderson Cancer Center, MOAD regimen: methotrexate, vincristine, pegylated L asparaginase, dexamethasone, MOF: multi-organ failure, Ph-: Philadelphia chromosome -ve,

Table 2

Results of relevant investigations done on the patients described in this study

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
MRI brain	-	-	Areas of T2/FLAIR hyperintensity with focal restricted diffusion involving bilateral centrum semiovale/corona radiata, right greater than left	Extensive leuko-encephalopathy	Normal	T2/FLAIR abnormalities with enhancement in R inf. frontal lobe. Abnormal enhancement pineal and L in internal auditory canal	No evidence leuko-encephalopathy
MRI spine	Diffuse enhancement of the distal conus and the nerve roots of the cauda equina	Diffuse enhancement along the conus medullaris and around the cauda equina	T2 hyperintensity along dorsal columns of T & L spine	T2 hyperintensity along dorsal and lat spine, dorsal columns C-spine	Expansion of cord at T3-8. T2 hyperintensity along dorsal columns from cervical to thoracic region	Diffusely expanded cord with abnormal T2 signal abnormality of the dorsal columns from the cervical cervical to terminale	T2 signal abnormality in C and T spine
EMG	(Day 13) Severe motor> sensory generalized (worse distally) polynuropathy mostly axonal	(Day 15) Normal EMG (5 months) Severe axonal neuropathy or anterior horn cell disease	N/A	N/A	(Day 60) Mild axonal predominantly motor neuropathy (Day 77) Moderate predominantly axonal motor>sensory neuropathy with some demyelinating features	(Day 43) Severe chronic and ongoing sensorimotor polynuropathy	(Day 39) Mild distal sensorimotor axonal polyneuropathy
PET CT	No definite leptomeningeal or IT hypermetabolism	No definite leptomeningeal or IT hypermetabolism	N/A	No definite leptomeningeal or IT hypermetabolism	No definite leptomeningeal or IT hypermetabolism	N/A	No definite leptomeningeal or IT hypermetabolism
CSF	WCC:16, RBC: 4450, protein: 149 → 330 (over 2 weeks), glucose: 221, cytology:-ve (<4) Flow cytometry: -ve	WCC:0, RBC: 1, protein: 82 → 154 (over 1 month), glucose:59, cytology: -ve (<4) Flow cytometry: N/A	WCC:0, RBC: 14875, protein: 99 → 30 (over 2 weeks), glucose: 51, cytology:-ve (<5) Flow cytometry: N/A	WCC:0, RBC: 5, Protein: 40 → 68 (over 2 weeks), glucose: 91, cytology: -ve (<3) Flow cytometry:-ve	WCC:0, RBC: 25, protein: 65 → 453 (over 3 months), glucose: 60, cytology: -ve (<13) Flow cytometry: N/A	WCC:5,RBC: 210, protein: 200 , glucose: 58, cytology: -ve (<3) Flow cytometry: -ve	WCC:0, RBC:4, protein: 55 → 105 (over 2 months), glucose:65, cytology:-ve (<5) Flow cytometry: -ve
CSF PCR HSV, HSV6, CMV, VZV, West Nile,	-ve,N/A,-ve,-ve, N/A, N/A	-ve, N/A, -ve, -ve, -ve, -ve	-ve, -ve,-ve, -ve, -ve, -ve	-ve,-ve,-ve,-ve, N/A, -ve	-ve,-ve,-ve,-ve, N/A, N/A	-ve, -ve, -ve, -ve, N/A, N/A	-ve, -ve, -ve, -ve, N/A, -ve

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
toxoplasma							
CSF fungal assays: Cryptococcal Ag	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Vit B12, MMA, copper, folate, homocysteine	790,N/A,N/A, 9.4, N/A	278,0.26, 1.29,N/A,N/A	235, 0.09, 0.91, 50.2, 37.7	514, 0.24, N/A, 6.8 , 13.9	335,0.17, N/A, 12.3, 14	1312,0.1,N/A, 12.8, 9.2	1329,0.15, N/A, 13.2, 4.3
CSF MBP	-	-	-	235.5	-	-	481.30

* Abbreviations: Ag: Antigen, CMV: Cytomegalovirus, CSF: Cerebrospinal fluid, EMG: Electromyography, HSV: Herpes Simplex Virus, MBP: Myelin Basic Protein, MMA: Methylmalonic acid, N/A: not available, PET: Positron Emission Tomography, PCR: Polymerase Chain Reaction, RBC: Red Blood Cells, Vit: Vitamin, VZV: Varicella Zoster Virus, WCC: White Cell Count

* Results marked in red indicate abnormal values.

* In all 7 patients, an infectious workup in the CSF was negative