Prevention of Neurotoxicity by High-dose Folinic Acid Rescue after High-dose Methotrexate and Intrathecal Methotrexate without Compromising Cure inspite of Previous Transient Leukoencephalopathy after Intrathecal Methotrexate

Dear Editor,

Methotrexate (MTX) is a frequently used chemotherapeutic agent in the treatment of childhood acute lymphoblastic leukaemia (ALL) and lymphoma. Besides oral and intravenous MTX, intrathecal MTX is an essential component of chemotherapy for ALL and is effective in preventing recurrences of central nervous system (CNS) leukaemia. Acute, subacute and chronic neurotoxicity have been observed after the administration of high-dose intravenous and/or intrathecal MTX.[1] The incidence varies with the route of administration, with less than 10% of those treated intravenously developing some neurotoxicity compared with up to 40% of patients treated intrathecally in combination with intravenous therapy.[2]

Case Report

A 10-year-old boy was diagnosed with pre-B ALL. There was no CNS involvement at diagnosis. The leukaemia remitted after induction chemotherapy with prednisone, vincristine and L-asparaginase according to the MRC ALL97/revised 99 Protocol for standard risk ALL. During week 22 of treatment, delayed intensification 1, he developed sudden onset quadriparesis (left more than right), numbness of upper limbs, slurred speech, and expressive dysphasia 3 days following his 8th intrathecal MTX of 12 mg. Oral thioguanine and subcutaneous cytarabine were concomitantly given at that time. A physical examination revealed hypotonia, areflexia and muscle power of three-fifth of all limbs. A cerebrospinal fluid (CSF) examination taken 6 days after the intrathecal MTX did not reveal any evidence of CNS leukaemia or infection (CSF: total protein - 427 mg/L, glucose - 2.8 mmol/L, cell count - 0/cmm). MTX level was not performed on the CSF. His clinical condition improved spontaneously, and 6 days after admission the neurological deficit had completely resolved. Magnetic resonance imaging (MRI) of the brain performed 16 days after the intrathecal MTX revealed bilateral white matter hyperdensity in the frontal lobes at the level of corona radiata extending to the centrum semiovale on T2-weighted images and fluid-attenuated inversion recovery images (FLAIR) (Figs. 1a and 1b). These clinical and MRI findings were in keeping with MTX-induced leukoencephalopathy. He received a further full dose of intrathecal MTX without any complications at week 32 and week 36 of treatment. However, he developed mild left-sided hand tremor at rest

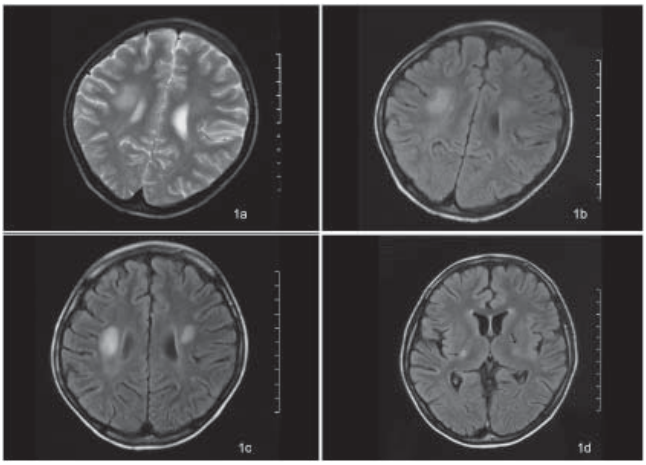

Fig 1. MRI scan at presentation showed bilateral white matter hyperdensity in the frontal lobes at the level of corona radiata extending to the centrum semiovale on T2-weighted images and T2-FLAIR (Fig. 1a and 1b). MRI scan at recurrence of MTX neurotoxicity showed bilateral deep white matter, basal ganglia and thalamic hyperdensity on T2-weighted FLAIR (Fig. 1c and 1d)

and on intention 5 days following intrathecal MTX in week 37 of treatment, delayed intensification 2, consisting of oral thioguanine and subcutaneous cytarabine co-medication. By then, he had received a total cumulative intrathecal MTX dose of 132 mg. Besides the tremor, the rest of the neurological examination was normal. CSF examination on day 7 after the intrathecal MTX did not reveal any evidence of CNS leukaemia or infection (CSF: total protein - 330 mg/L, glucose - 2.5 mmol/L, cell count - 0/cmm). The tremor gradually improved but completely resolved only 6 weeks later. MRI of the brain revealed bilateral deep white matter, basal ganglia and thalamic hyperdensity on T2-weighted FLAIR (Figs. 1c and 1d). Unfortunately 3 months later, the leukaemia relapsed in the CNS 51 weeks after diagnosis. He received high-dose intravenous MTX 1 gm/m^2, and intrathecal therapy (12 mg MTX) according to the relapsed leukaemia protocol. The patient did not receive radiotherapy. He was commenced on intravenous folinic acid 100 mg/m^2 at 48 hour after starting on intravenous MTX and given 3 hourly for 8 doses followed by 100 mg/m^2 6 hourly for 4 doses. He received same folinic acid rescue after each course of high-dose intravenous MTX. There was no recurrence of symptoms of MTX neurotoxicity during and after 6 courses of high-dose intravenous MTX and 9 intrathecal MTX. A repeat MRI of the brain was not

performed. At the time of this report, the patient is currently in remission 84 weeks after his CNS relapse.

Discussion

The clinical manifestation of quadriparesis and numbness of upper limbs of our patient correlated with the involvement of motor and sensory fibres in the corona radiata. The tremor correlated with the involvement of the basal ganglia. His language disturbance could be explained by altered mental status due to frontal lobes involvement. The neuro-radiological changes were less likely due to steroid or vincristine neurotoxicity as prednisone was not given concomitantly during that time, and previous dose of vincristine was given 3 weeks before the onset of symptoms.

The exact pathophysiology of MTX neurotoxicity is still not understood but it is believed that MTX can induce direct toxic effects to the CNS by damaging the neuronal tissue.[1] Also, additions such as preservatives could possibly induce or aggravate neurological symptoms.[3] Therefore, intrathecal MTX should always be of the preservative-free solution. Our patient received preservative-free MTX. This case illustrates that recurrent MTX neurotoxicity in a child receiving intrathecal MTX was reversible on 2 occasions. Why it occurred only in these 2 instances and not in the other 9 doses of intrathecal MTX that he received, was unclear. Recurrence of MTX neurotoxicity was not seen in this patient, even after the combination with high-dose intravenous MTX, using high-dose folinic acid rescue. Although some therapists may feel that the use of high-dose MTX is contraindicated after transient leukoencephalopathy following intrathecal MTX, we have shown that this treatment is possible without toxicity if adequate dose folinic acid is used. This does not seem to have compromised the treatment results since his initial CNS relapse was after 51 weeks. Previous reports by Cohen et al[4-6] suggest that the administration of high-dose folinic acid to prevent neurotoxicity did not interfere with its ability to kill the leukaemic cells and without effecting prognosis. At the time of this report, the treatment including high-dose MTX has kept the patient free of relapse for 84 weeks.

REFERENCES

1. Vezmar S, Becker A, Bode U, Jaehde U. Biochemical and clinical aspects of methotrexate neurotoxicity. Chemotherapy 2003;49:92-104.
2. Mahoney DH, Shuster JJ, Nitscke R, Lauer SJ, Steuber CP, Winick N, et al. Acute neurotoxicity in children with B-precursor acute lymphoblastic leukemia: an association with intermediate-dose intravenous methotrexate and intrathecal triple therapy: a Pediatric Oncology Group study. J Clin Oncol 1998;16:1712-22.
3. Dunkelman H, Earl HM, Twelves C. Acute reversible neurological deficit following intrathecal chemotherapy. Cancer Chemother Pharmacol 1991;27:329-30.
4. Cohen IJ, Stark B, Kaplinsky C, Weitz R, Matz S, Lerman P, et al. Methotrexate-induced leucoencephalopathy is treatable with high-dose folinic acid: A case report and analysis of the literature. Pediatr Hematol Oncol 1990;7:79-87.
5. Cohen IJ. Defining the appropriate dosage of folinic acid after high-dose methotrexate for childhood acute lymphatic leukemia that will prevent neurotoxicity without rescuing malignant cells in the central nervous system. J Pediatr Hematol Oncol. 2004;26:156-63.
6. Cohen IJ. Prevention of high-dose-methotrexate neurotoxicity by adequate folinic acid rescue is possible even after central nervous system irradiation. Med Hypotheses. 2007;68:1147-53.

Alias Hamidah,[1] BMedSc, MD, MMed(Paed), Raja Juanita Raja Lope,[1] MBBS, MRCPCH(UK), Zarina Abdul Latiff,[1] MBBS, MMed(Paed), Zulfiqar M Anuar,[2] MBBS, MMed(Rad), Rahman Jamal,[1] MRCP, PhD(UK)

[1] Department of Paediatrics, Faculty of Medicine, National University of Malaysia, Kuala Lumpur, Malaysia
[2] Department of Radiology, Faculty of Medicine, National University of Malaysia, Kuala Lumpur, Malaysia

Address for Correspondence: Dr A Hamidah, Department of Paediatrics, Faculty of Medicine, Hospital UKM, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia;
Email: midalias@ppukm.ukm.my