Mefloquine Treatment in a Patient Suffering from Progressive Multifocal Leukoencephalopathy after Umbilical Cord Blood Transplant

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Abstract

We report herein the case of a 37-year-old man who developed probable progressive multifocal leukoencephalopathy (PML) following an umbilical cord blood transplant. The patient showed favorable clinical, neuroradiological and virological responses after treatment with mefloquine, an anti-malarial drug. Mefloquine may offer some benefits as a treatment for PML in patients with or without human immunodeficiency virus type-1 infection. This report highlights the need to gather sufficient data to confirm the efficacy of mefloquine against this devastating viral disease of the central nervous system.

Key words: progressive multifocal leukoencephalopathy, mefloquine


Introduction

Progressive multifocal leukoencephalopathy (PML) is a subacute demyelinating disease of the brain caused by the JC virus (JCV) and occurring mainly in immunocompromised patients. In acquired immunodeficiency syndrome (AIDS)-related PML, long-term survival has been reported in patients receiving highly active antiretroviral therapy (HAART) (1). However, in comparison with AIDS-related PML, the prognosis of non-AIDS PML is very poor and therapeutic options are few and often ineffective. We report herein the case of a patient with an underlying hematological disease who developed PML following umbilical cord blood transplantation, and subsequently showed favorable clinical, virological and imaging responses after mefloquine treatment.

Case Report

In January 2002, a 37-year-old man diagnosed with leiomyosarcoma of the right tibia was treated with tumor resection and 5 courses of high-dose methotrexate (MTX), Adriamycin and cisplatin. Complete remission was achieved by May 2006. At that time, chemotherapy-related acute myelocytic leukemia (AML) developed and was treated using 1 cycle of idarubicin and cytarabine (Ara-C) consolidated with high-dose Ara-C. However, relapses were identified in bone marrow and the central nervous system (CNS) and he was treated using Ara-C, aclarubicin and filgrastim with 12 intrathecal administrations of MTX/Ara-C/prednisolone (PSL). Two umbilical cord blood transplantations were performed in July and August 2007 with reduced-intensity conditioning comprising fludarabine, melphalan and total body irradiation. Graft-versus-host disease (GvHD) prophylaxis was performed using tacrolimus. The patient experienced human herpes virus-6 related limbic encephalitis 1 month after the last transplantation, but this was successfully treated using foscarnet at 90 mg/kg/day for 59 days. Complete remission was identified on bone-marrow examination, and immunosuppression by tacrolimus was tapered off by November 2007. Intrathecal administration of Ara-C/PSL was continued every 2 weeks until July 2008, due to meningeal involvement by AML before transplantations. Psychomotor slowing developed in September 2008 and worsened over the subsequent 2 months. No medications were administered at that time. Clinical examination revealed expressive aphasia and mild right hemiparesis. Tendon reflexes were brisk on the right
with an extensor plantar response in the right foot. Brain magnetic resonance imaging (MRI) performed on October 29, 2008, showed multiple frontotemporal hyperintense white matter lesions on T2-weighted and fluid-attenuated inversion-recovery (FLAIR) imaging, more prominent on the left side than on the right. Diffusion-weighted imaging (DWI) showed signal hyperintensities throughout the high-intensity areas seen on T2-weighted and FLAIR imaging (Fig. 1A, 1B). No mass effect or contrast enhancement was seen on T1-weighted imaging. The abnormal signal intensities were not seen in the bilateral mesial temporal lobes. Cerebrospinal fluid (CSF) showed mild pleocytosis (6 cells/mm³), normal levels of protein (35 mg/dL) and glucose (54 mg/dL), and normal results on cytological examination. Polymerase chain reaction (PCR) for JCV in the CSF yielded positive results, showing 911,175 copies/mL according to real-time PCR (Fig. 2). White blood cell (WBC) count was 6.5×10⁹/μL, with 46.7% lymphocytes, and CD4 (+) lymphocyte count was 419 cells/μL with a CD4/CD8 ratio of 0.63. Other laboratory studies showed normal results, except for increased soluble interleukin-2 receptor levels (1,084 U/mL; normal, 190-650 U/mL). Whole-body ¹⁸F-2-fluoro-2-deoxyglucose positron emission tomography showed an area of low uptake consistent with demyelination in the left cerebral white matter and high uptake foci suggesting malignant disease in the cervical lymph nodes, liver, and thoracic and pelvic bones. Bone marrow aspiration from the ilium did not show any relapse of AML. Computed tomography of the liver showed an enhanced mass lesion measuring 5×5×4 cm. Biopsy of the liver showed leiomyosarcoma with suspected metastasis to the liver. Probable PML associated with multiple metastatic leiomyosarcoma was diagnosed. The condition of the patient gradually worsened to complete right hemiplegia, right homonymous hemianopsia, dysphagia and
lethargy. Follow-up brain MRI in early December 2008, showed marked extension of the cerebral lesion (Fig. 1C, 1D). In mid-December 2008, in an attempt to halt the neurological deterioration, administration of mefloquine hydrochloride tablets (Mephaquine Hisamitsu; Hisamitsu Pharmaceutical, Tosu, Japan) was started at 275 mg/day orally for 3 days, then 275 mg once weekly up to 6 months, as a modification of the Biogen Idec mefloquine treatment protocol taken from the clinicaltrials.gov website (2). This drug was administered after obtaining informed consent from the family of the patient and approval from the ethics board of our hospital. Brain MRI in early January 2009, showed further extension of the lesion (Fig. 1E, 1F), but symptoms stabilized and then gradually started to improve. By mid-January 2009, the patient had started to watch television, respond to simple commands and eat jelly. Follow-up real-time PCR for JCV in mid-January 2009 (1 month after the start of mefloquine therapy) showed a marked reduction of JCV viral load in CSF to 743 copies/mL. Brain MRI in early February 2009, showed arrested progression with appearance of hypointense zones in both frontal lobes on FLAIR imaging (Fig. 1G, 1H). In addition, signal hyper-intensities had disappeared on DWI. Real-time PCR for JCV in early March 2009 (3 months after the start of mefloquine therapy) showed levels below the limits of detection in CSF (Fig. 2). His neurological condition stabilized with complete right hemiplegia and righthomonymous hemianopsia. Follow-up MRI 5 months after initiation of treatment (May 2009) showed no progression of the lesions with atrophy of both frontal lobes (Fig. 1I, 1J). However, JCV was again detected in CSF (viral load, 192 copies/mL) on maintenance dose. The lymphocyte count at that time was 3,400/μL and CD4 (+) lymphocyte count was 966 cells/μL with a CD4/CD8 ratio of 0.64. JCV viral load increased to 566 copies/mL in CSF in July 2009. A second cycle of mefloquine therapy was started in mid-July and JCV PCR of CSF yielded negative results again within 1 month. CD4 (+) lymphocyte count was 510 cells/μL with a CD4/CD8 ratio of 0.72. MRI of the brain showed no changes and no new sites of active disease. At no stage during the clinical course did brain MRI show enhancement on T1-weighted imaging after administration of gadolinium contrast. The patient was discharged home and has remained neurologically and radiologically stable (Fig. 1K, 1L) at home with a burden of leiomyosarcoma for >20 months since the onset of symptoms, despite stopping mefloquine intake 2 months after the start of the second cycle.

**Discussion**

We report the case of a patient with AML who developed probable PML following umbilical cord blood transplantation. JCV load in CSF was monitored in this patient under treatment with the anti-malarial mefloquine.

To date, no satisfactory treatments for PML have been identified. Although spontaneous partial recovery and prolonged survival have been recognized in PML (3), the disease is almost invariably relentlessly progressive and 80% of patients die within 9 months (4). Reduction or withdrawal of immunosuppressants in patients with non-AIDS PML and the use of HAART in AIDS-related PML are the only known interventions that may allow immune reconstitution and control of pathological viral activity. In AIDS-related PML, HAART stops the progression of leukoencephalopathy and allows long-term survival (>12 months) in about half of those who receive it (1). However, neurological deficits frequently persist because of irreparable loss of brain tissue, and only a few patients functionally improve. In addition, PML may worsen paradoxically and occasionally become fatal despite potent HAART in the setting of immune recon-
stition inflammatory syndrome (5). A significant number of patients with AIDS-related PML thus do not appear to receive substantial benefit from HAART. In comparison with AIDS-related PML, the prognosis of non-AIDS PML is dismal, particularly among transplant recipients, with an average survival of only a few months (6, 7). Withdrawal or dose reduction of immunosuppressive drugs does not necessarily improve outcomes in patients with non-AIDS PML.

Several medications with in vitro activity against JCV have been employed in combination with HAART or alone in patients with AIDS-related and non-AIDS PML, but have unfortunately proven largely ineffective, although some case reports have described various outcomes. Such agents have included interferons, DNA topoisomerase inhibitors, cytarabine, and cidofovir (8). Since the 5-HT2A serotonin receptor has been found to act as a receptor for JCV in glial cells (9), the use of serotonin receptor blockers that are selective for the 5-HT2A receptor, such as mirtazapine and risperidone, appears warranted (8). However, these agents have not yet been demonstrated to improve outcomes in large prospective studies. The anti-malarial drug mefloquine has very recently been recognized to have anti-JCV activity at non-toxic concentrations with in vitro culture, and passes the blood-brain barrier to achieve concentrations in the brain above the level inhibiting JCV replications in vitro (10). To the best of our knowledge, this drug has not been used in clinical practice for PML, and a clinical trial is now underway. We therefore attempted treatment with mefloquine according to the dose and administration schedules for mefloquine need to be reconsidered.

The successful outcome in the present patient with mefloquine offers a new therapeutic strategy worthy of further trial in other patients with PML, in an attempt to identify useful treatments for this all-too-frequently fatal disease.

Mefloquine is prescribed as a prophylaxis and/or treatment for malaria, and has already been approved for human use and the safety profile of mefloquine is well known. PML is a rare disease, so multi-centric efforts are necessary to gather sufficient data to confirm the efficacy of mefloquine. And a randomized multicenter clinical trial is currently underway to assess the effect of mefloquine on JCV DNA levels in CSF (2).

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References

9. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. Science 306: 88-

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