Novel treatment (new drug/intervention; established drug/procedure in new situation)

Progressive multifocal leucoencephalopathy after autologous bone marrow transplantation: a treatment option

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Summary

A patient with multiple myeloma was treated with high-dose chemotherapy followed by two autologous bone marrow transplantations (ABMTs). Nine months after the second ABMT the patient complained of severe left hemiparesis, paraesthesias, left homonymous visual field defects and gait ataxia. She was diagnosed with progressive multifocal leucoencephalopathy (PML) confirmed by detection of JC virus (JCV) DNA and prescribed cidofovir every other week and mirtazapine daily. Her symptoms and signs remained stable and after 6 months the JCV DNA was undetectable in the cerebrospinal fluid. Repeated MRI scans demonstrated the stabilisation of demyelinating lesion volume; after more than 2 years of follow-up the patient's neurological examination does not show significant variations. Combination of cidofovir and mirtazapine may be helpful in the treatment of PML in HIV-negative patients.

BACKGROUND

Progressive multifocal leucoencephalopathy (PML), a demyelinating disease of the central nervous system (CNS) caused by JC virus (JCV), is a rare complication described in immunocompromised patients. JCV infection is frequent in the general population and usually occurs completely asymptomatic. After infection, JCV, a DNA polyomavirus, may remain latent for many years in kidney cells and in the CNS and is under constant surveillance of the cellular immune system.¹

In some patients, the reactivation of the viral replication leads to the clinical picture of PML, frequently including hemiparesis, apathy and confusion. The incidence of PML in HIV-patients is 4–7%.¹ PML disease usually evolves over days to weeks and is mostly fatal with 90% of patients dying within 12 months, but long-term survival has been also documented,² with or without HIV as the underlying immunodeficiency disorder. Among HIV-negative patients, PML is less common and is usually linked to facilitating factors such as putative genetic susceptibility factors or a prolonged immunosuppressive or cytotoxic treatment for various disorders or with organ or haematopoietic stem cell transplantation. Recently, over 35 cases of PML have been described after long-term treatment with natalizumab for multiple sclerosis.¹

CASE PRESENTATION

We report a 63-year-old woman suffering from symptomatic immunoglobulin G- λ light chain multiple myeloma diagnosed in November 2006. After a 4-month treatment with thalidomide and dexamethasone, high-dose cyclophosphamide (4 g/m²) and granulocyte colony-stimulating

factor stimulation were used to mobilise haemopoietic stem cells, which were subsequently collected from peripheral blood. The patient was treated with tandem autologous stem cell transplantation after conditioning with high-dose melphalan (200 mg/m²) in April and September 2007 achieving a complete remission of the myeloma. Maintenance therapy with thalidomide (50 mg/day) was started 3 months later.

In August 2008, the patient was admitted to our hospital because of numbness and tingling in the legs, left hemiparesis, ataxia, nausea and apathy.

INVESTIGATIONS

On admission, all routine lab tests including screening for autoimmune diseases and HIV were negative. A brain CT scan showed a hypodense lesion in the right parietal lobe, and on MRI scan lesions suggestive of PML were detected (figure 1A).

Subsequently, lumbar puncture revealed a normal cerebrospinal fluid (CSF) cell count and protein isoelectric focusing showed identical oligoclonal bands in the CSF and in the serum.

JCV DNA was detected by PCR in the CSF and in the peripheral blood, with a mutation in the DNA coding for the major capsid protein involved in recognition of the cellular receptor (Arg75Lys in the BC loop of viral surface protein (VP1)).³

TREATMENT

Maintenance therapy with thalidomide was discontinued and after a review of the available literature⁴ we focused on the combination of two drugs.

Figure 1 Disease evolution in MRI scans. Fluid-attenuated inversion recovery sequences acquired in the coronal plane, from baseline to 22 months follow-up. (A) On admission: diffuse subcortical and deep white matter hyperintensity in periventricular areas and mainly in right frontal-parietal lobes. (B) At discharge: contralateral white matter involvement is extended. (C) Improvement of white matter alterations and widening of sulcal and ventricular spaces suggesting brain atrophy. At this time the JC virus DNA was undetectable in the cerebrospinal fluid. (D) The last scan shows severe atrophy with hydrocephalus, but stable white matter lesions.

Cidofovir, approved for cytomegalovirus infection, has been tested in some HIV-negative patients with controversial results.^{5 6}

There are open label studies supporting a therapeutic action of cidofovir^{7 8} but its efficacy has not been proven by randomised controlled clinical trials (RCTs).⁹

Mirtazapine is an α -2-adrenergic, 5HT_{2A} and 5HT₃-receptor antagonist that crosses the blood-brain barrier. The drug is approved as an antidepressant; its binding properties to 5HT_{2A}, which also acts as a cellular receptor for JCV,¹⁰ might confer a protection against the spread of JCV infection to adjacent glial cells as suggested by several case reports.^{11–13}

The Institutional Ethics Committee approved the off-label treatment with cidofovir 5 mg/kg intravenous once weekly for 2 weeks and then once every other week plus probenecid 2 g per day and mirtazapine 30 mg per day.

This treatment was well tolerated and 1 month later, in September 2008 (figure 1B), the neurological examination confirmed left homonymous hemianopsia, hemineglect, left hemiplegia and hypoaesthesia. The patient concluded intravenous cidofovir in October 2008, but was kept on mirtazapine at the initial dose.

Lumbar puncture was repeated in February 2009 (figure 1C). Surprisingly, CSF analysis was normal and no JCV genome was detected by PCR.

OUTCOME AND FOLLOW-UP

After a more than 2-year follow-up (figure 1D) the patient's neurological condition remained stable after maintenance treatment with mirtazapine 30 mg per day with residual spastic left hemiplegia, left homonymous hemianopsia and mild ipsilateral hypoaesthesia despite progression of brain atrophy on MRI.

DISCUSSION

Restoring the immune response in the host is one of the crucial steps in PML therapy. Accordingly, in HIV-patients, highly active antiretroviral therapy is the first treatment option for PML.

In the less common HIV-negative PML patients, in addition to the early discontinuation of immunosuppression, several drugs have been tested and in the natalizumab-treated patients plasma exchange has also been recommended¹⁴ to eliminate circulating monoclonal antibodies, although this has not yet been formally tested.¹⁵

Clinical reports on the use of mirtazapine in small numbers of HIV patients (three clinical improvements, one stable)^{12 13} or in HIV-negative patients¹⁶ are encouraging; however, it is difficult to assess the effects of mirtazapine on clinical improvement due to the various drug combinations used in the reported cases.

In our patient, the combination of the virostatic drug cidofovir and the antidepressant mirtazapine was satisfactory, as described in another reported case.¹⁷

The disappearance of JCV in the CSF following successful treatment was previously shown in both HIV positive¹⁸ and negative¹⁹ patients. In theory, the absence of detectable viral DNA in the host may be a favourable prognostic marker; however, so far there is no evidence about the timing and the real long-term impact.¹

Alternatively, the variability of the viral genome could change the pathogenicity and thereby the natural history of the disease. We cannot exclude the possibility that the favourable clinical course of our patient might also have been the consequence of a VP1 mutation, which appears to be critical for the development of PML, for example, the Arg75Lys mutation in the BC loop.³

Learning points

- ▶ Until RCTs become available, treatment of PML will continue to be based on instructive case descriptions in addition to the already generally accepted off-label recommendations. Based on this limited evidence and in view of the devastating nature of this disease, we recommend a combination of cidofovir plus mirtazapine for PML. RCTs should now be encouraged and are feasible if done as a world-wide effort.

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Competing interests None.

Patient consent Obtained.

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