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REVIEW

Novel treatments for progressive multifocal leukoencephalopathy

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Abstract

Progressive multifocal leukoencephalopathy is a rare demyelinating disorder of the CNS, caused by John Cunningham virus, that occurs in those with impaired immune systems. Existing treatment options are ineffective or unproven. This article reviews research into novel therapies: immune checkpoint-blocking antibodies (nivolumab and pembrolizumab), allogenic BK virus-specific T cell treatment and filgrastim. Results for these therapies in small clinical trials are promising, but further research is required to assess efficacy fully.

Key words: Filgrastim; Leukoencephalopathy; Multifocal; Nivolumab; Progressive; Pembrolizumab

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Introduction

Progressive multifocal leukoencephalopathy is a rare demyelinating disorder of the CNS caused by John Cunningham virus (JC virus), a neurotropic polyomavirus. JC virus is present in around 50% of the population, causing an asymptomatic latent infection in the renal tract and/or bone marrow (Sabath and Major, 2002). Failure of immune control allows penetration of the virus into the CNS, resulting in widespread oligodendrocyte lysis (Major et al, 2018), often with devastating consequences (Case study). The clinical presentation varies depending on the location and extent of demyelination, but symptoms often include muscle weakness, sensory deficit, hemianopia, cognitive dysfunction and coordination difficulties (Pavlovic et al, 2015).

Progressive multifocal leukoencephalopathy usually only affects those who are immunosuppressed (Clifford, 2015), with three associations accounting for 90% of cases:

1. Human immunodeficiency virus (HIV) infection
2. Immunosuppressing haematological malignancies
3. Patients with multiple sclerosis treated with natalizumab (Pavlovic et al, 2015).

Less commonly, progressive multifocal leukoencephalopathy is associated with organ transplantation, solid malignancies, sarcoidosis, autoimmune disorders and other immunosuppressant medications (such as prednisolone, dimethyl fumarate and rituximab) (Pavlovic et al, 2015; Maas et al, 2016).

Case study

A 67-year-old man presented with left-sided weakness and reduced left hand dexterity 4 months after an autologous stem-cell transplant for multiple myeloma. He had no other past medical history. A computed tomography scan of the head showed multiple areas of low attenuation and magnetic resonance imaging demonstrated numerous hyperintense T2 lesions within the subcortical white matter of both cerebral hemispheres. Over 6 months his clinical symptoms continued to progress such that he developed emotional lability, motion sickness, cognitive dysfunction and was unable to walk 2 metres unaided. An extensive set of investigations were performed to determine the cause. He was positive for JC virus, along with compatible clinical and radiological findings which met the diagnostic criteria for progressive multifocal leukoencephalopathy (Berger et al, 2013). In this case there was no scope to improve immune functioning and he was started on mirtazapine as a potential antiviral therapy. Despite this intervention he continued to deteriorate and died shortly afterwards (Bennett et al, 2020).

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The diagnostic criteria for progressive multifocal leukoencephalopathy are either characteristic findings on brain biopsy or a combination of the appropriate clinical symptoms, radiological features and the presence of JC virus in the CSF (Berger et al, 2013). Prognosis is poor in patients with progressive multifocal leukoencephalopathy unless immunosuppression can be reversed (Pavlovic et al, 2015). In a Swiss HIV cohort, infected patients who had progressive multifocal leukoencephalopathy had a 1-year mortality rate of 30%, even with highly active antiretroviral therapy, although this is much improved compared to the rate of 83% in the pre-highly active antiretroviral therapy era (Khanna et al, 2009). In those with multiple sclerosis treated with natalizumab, 77% are alive at 3 years, and in those with active immunosuppressing haematological malignancies just 10% are alive beyond 2 months (Pavlovic et al, 2015).

The restoration of CNS immunocompetence in patients with progressive multifocal leukoencephalopathy carries the risk of immune reconstitution inflammatory syndrome (McCarthy and Nath, 2010). This is defined as the paradoxical sudden worsening of the signs and symptoms of progressive multifocal leukoencephalopathy in the setting of immune reconstitution, often with contrast enhancement in the progressive multifocal leukoencephalopathy lesion on magnetic resonance imaging. The pathophysiological process in immune reconstitution inflammatory syndrome is thought to be high levels of inflammation causing damage to previously intact brain tissue; this can be fatal if significant vasogenic oedema occurs. Treatment of progressive multifocal leukoencephalopathy immune reconstitution inflammatory syndrome is with high dose corticosteroids to reduce CNS inflammation.

Existing treatments

Current treatment options for progressive multifocal leukoencephalopathy focus on restoring immune function through reversing exogenous immunosuppression. For example, patients with HIV are started on highly active antiretroviral therapy and patients on natalizumab have their treatment stopped, often using plasma exchange to more rapidly eliminate the drug from the circulation. However, in some circumstances, immunosuppression cannot be reversed, such as in patients with heart–lung transplants or patients with conditions causing intrinsic immunosuppression, such as sarcoidosis or primary immunodeficiency. In these situations, the only remaining therapeutic possibility is to attack the virus. Pavlovic et al (2015) reviewed these potential options, dividing them into antiviral agents, immune response modulators and immunisation strategies. As shown in Table 1, small-scale clinical trials have taken place for the following drugs: cytarabine, topotecan, cidofovir, mefloquine, interferon-alpha 2b and zidovudine; all have demonstrated negative or inconclusive results. Research for other drug options is limited to case studies and retrospective studies with no strong consensus. Identification of successful treatments is challenged by inadequate animal models, small patient numbers and rapid disease progression.

Treatment with interleukin-7 (IL-7) aims to boost depleted T-cell response. It is a cytokine which stimulates proliferation of cells in the lymphoid lineage and supports their maturation, survival and homeostasis (Pavlovic et al, 2015). Individual case studies have reported promising results of using IL-7 to treat those with progressive multifocal leukoencephalopathy and idiopathic lymphocytopenia (Alstadhaug et al, 2014; Harel et al, 2016; Miskin et al, 2016).

Novel treatments for progressive multifocal leukoencephalopathy

Research has begun to test novel immune-boosting agents in the treatment of progressive multifocal leukoencephalopathy. These comprise three main groups of therapies, all of which show promise:

1. Immune checkpoint-blocking antibodies (nivolumab and pembrolizumab)
2. Allogenic BK virus-specific T-cell treatment
3. Filgrastim.

Table 1. Medications used to treat progressive multifocal leukoencephalopathy

	Drug	Presumed mechanism	Efficacy in clinical trials
Antiviral agents	Mefloquine	Inhibits viral replication	Negative or inconclusive
	Mirtazepine	Blocks serotonin receptors	None
	Cidofovir	Inhibits infection	Negative
	Ganciclovir	Inhibits viral polymerases	None
	Topotecan	Inhibits replication	Inconclusive or poorly tolerated
	Cytarabine	Decrease replication	Negative
Immune response modulators	Interferon A	Increases cell-mediated immunity	Negative
	IL-2	Increases T cell function	None
	IL-7	Increases lymphoid proliferation	None
	Maraviroc	Decreases inflammation	None
	Corticosteroids	Decreases inflammation	None
Immunisation strategies	Intravenous immunoglobulin	Uncertain	None
	Anti-JCV Ab	Neutralises virus	None
	Anti-JC virus vaccine	Neutralises virus	None

From Pavlovic et al (2015)

Immune checkpoint-blocking antibodies: nivolumab and pembrolizumab

The immune system has a complex set of checks and balances, known as immune checkpoints, which avoid damage caused by over-stimulation. One aspect of this process involves programmed cell death-1 (PD-1), a negative immune regulator expressed on activated T cells. Nivolumab and pembrolizumab are anti-cancer drugs that block this inhibitory pathway, reinvigorating T-cell activity, and thereby boosting the immune response against cancer (Wykes and Lewin, 2018). Both drugs have similar pharmacological features, differing on the precise PD-1 epitope recognised, and are licensed in the UK for the treatment of melanoma, Hodgkin's lymphoma, and non-small cell lung cancer (Koralnik, 2019).

An indication of the potential benefit of immune checkpoint inhibitors against JC virus came from the finding that PD-1 expression is elevated on the CD4+ and CD8+ T lymphocytes of patients with progressive multifocal leukoencephalopathy, and is especially elevated on JC virus-specific CD8+ T cells (Tan et al, 2012). Initial clinical studies have been promising, with Cortese et al (2019) presenting a case series of eight patients treated with pembrolizumab for progressive multifocal leukoencephalopathy. These patients had a mixture of underlying conditions including HIV, haematological malignancies (chronic lymphocytic leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma), and idiopathic lymphopenia. All eight patients showed down-regulation of lymphocytes in the peripheral blood and CSF before pembrolizumab treatment. After pembrolizumab treatment five patients showed clinical improvement or stabilisation, with concomitant reduction in CSF JC viral load and increased in-vitro CD4+ and CD8+ anti JC virus activity. In three of the eight patients there was no clinical improvement and no change in viral load. In retrospect, one of the five patients showing clinical improvement was noted to have had some clinical, radiological and virological stabilisation of progressive multifocal leukoencephalopathy before treatment. Two of the five patients showing clinical improvement had HIV and were concurrently started on antiretroviral therapy which will have contributed to immune system restoration (Koralnik, 2019). None of the patients had complete resolution of the progressive multifocal leukoencephalopathy brain lesions.

Promising results with pembrolizumab or nivolumab have also been seen in individual case studies, with outcomes ranging from partial to full recovery (Audemard-Verger et al, 2019; Hoang et al, 2019; Uzunov et al, 2019; Walter et al, 2019). Perhaps unsurprisingly,

patients treated early seem to do better than those treated with late-stage disease. A case series of nivolumab usage in three patients with kidney transplants and progressive multifocal leukoencephalopathy showed poor outcomes, with all three dying shortly after diagnosis (Medrano et al, 2019). Interestingly, these three patients and the three patients with no clinical improvement described by Cortese et al (2019) all had significant lymphopenia, suggesting the use of immune checkpoint-blocking antibodies may be limited in this subset of patients. These studies are summarised in Table 2. There are no reports of successful use of immune checkpoint inhibitors in patients who have had organ transplants (Focosi et al, 2019).

The development of immune reconstitution inflammatory syndrome in patients with progressive multifocal leukoencephalopathy who had been treated with immune checkpoint inhibitors was variable. In the cases showing clinical improvement, some did show immune reconstitution inflammatory syndrome (Hoang et al, 2019; Rauer et al, 2019) but this was not universal (Audemard-Verger et al, 2019; Cortese et al, 2019; Walter et al, 2019). Thus, immune reconstitution inflammatory syndrome does not appear to be a prerequisite for clinical improvement, although differentiating between progressive multifocal leukoencephalopathy immune reconstitution inflammatory syndrome and progressive multifocal leukoencephalopathy alone can be challenging. It should be noted that none of the patients with poor outcomes developed immune reconstitution inflammatory syndrome, indicating that immune reconstitution inflammatory syndrome may be an indicator of a positive outcome.

Other side effects of immune checkpoint inhibitors in progressive multifocal leukoencephalopathy cohorts include rashes (Cortese et al, 2019), diarrhoea (Rauer et al, 2019) and myositis (Uzunov et al, 2019). In cancer cohorts immune checkpoint inhibitors are associated with serious side effects involving all organ systems (Heinzerling and Goldinger, 2017), including myasthenia gravis and cardiotoxicity (Hottinger, 2016; Suzuki et al, 2017). One case report details progressive multifocal leukoencephalopathy developing after treatment with nivolumab in a patient with refractory stage IV Hodgkin lymphoma (Martinot et al, 2018), although it cannot be determined whether progressive multifocal leukoencephalopathy was caused by nivolumab or the underlying immunocompromised state.

There does not appear to be a discernible difference between nivolumab and pembrolizumab and there are no reports on other immune checkpoint inhibitors such as ipilimumab, atezolizumab, avelumab or durvalumab. All these treatments are expensive and use in patients with progressive multifocal leukoencephalopathy is currently unlicensed.

Allogeneic BK virus-specific T cells

BK is a polyomavirus closely related to JC virus, causing renal tract infections in immunocompromised patients after stem-cell or solid organ transplant. A novel treatment for BK virus infections involves screening donated blood for BK-specific T-cells, clonally expanding these cells, and transfusing these into BK-infected immunocompromised patients, with promising results (Tzannou et al, 2017). It was therefore postulated that T-cells developed against BK virus may also be effective against JC virus, because of the similarities between these related pathogens. This theory was tested in three patients with different underlying conditions: acute myeloid leukaemia treated with cord blood transplant, myeloproliferative neoplasm treated with ruxolitinib, and HIV treated with highly active antiretroviral therapy (Muftuoglu et al, 2018). Each patient received HLA-matched BK virus-specific T-cells. In two patients (myeloproliferative neoplasm treated with ruxolitinib and HIV treated with high active retroviral therapy) there was significant clinical improvement. JC virus in the CSF disappeared and lesions on magnetic resonance imaging decreased. Both patients developed immune reconstitution inflammatory syndrome. However, these results are confounded by the respective discontinuation of ruxolitinib and the commencement of anti-retroviral therapy. The third patient stabilised but did not improve, with concomitant reduction – but not clearance – of CSF JC virus. She died 8 months after starting treatment. The authors postulate that the lack of clinical improvement in this patient may have been the result of late initiation of treatment for progressive multifocal leukoencephalopathy.

Table 2. Outcomes of patients with progressive multifocal leukoencephalopathy treated with immune checkpoint inhibitors

Treatment	Age and sex	Underlying condition(s)	Time between onset of symptoms and treatment initiation	CSF viral load at treatment onset (copies per ml)	PML IRIS	Outcome	Reference
Pembrolizumab	67 M	Chronic lymphocytic leukaemia	15 months	232	No	(=) Symptoms stabilised before treatment	Cortese et al (2019)
Pembrolizumab	78 M	Chronic lymphocytic leukaemia	7 months	6044	No	(+) Confusion, language and ataxia improved slightly	Cortese et al (2019)
Pembrolizumab	48 F	HIV/AIDS	6 months	63	No	(+) Improvement in language and cognition, independent in activities of daily living	Cortese et al (2019)
Pembrolizumab	69/F	Non-Hodgkin lymphoma	12 months	26 494	No	(-) Clinical deterioration	Cortese et al (2019)
Pembrolizumab	31/M	Idiopathic lymphopenia	2 months	5248	No	(+) Improvement in confusion and increased independence with activities of daily living	Cortese et al (2019)
Pembrolizumab	62/F	Idiopathic lymphopenia, common variable immunodeficiency	3 months	28 350	No	(-) Clinical deterioration and became wheelchair bound	Cortese et al (2019)
Pembrolizumab	70/M	Hodgkin's lymphoma	2 months	261	No	(+) Modest improvements in gait and speech	Cortese et al (2019)
Pembrolizumab	58/M	HIV/AIDS	12 months	286	No	(+) Subjective clinical improvement	Cortese et al (2019)
Pembrolizumab	42/M	Idiopathic primary immunodeficiency	5 months	38	No	(-) Clinical deterioration	Kupper et al (2019)
Pembrolizumab	38/M	Combined immunodeficiency and Behçet's disease	4 weeks	2 561 955	No	(-) Died 4 weeks after treatment initiation	Pawlitzki et al (2019)
Pembrolizumab	Unknown /M	Variable immunodeficiency and diffuse B cell lymphoma	10 weeks	119 000	Yes	(+) Speech recovery but ongoing psychomotor slowing, aphasia and disorientation	Rauer et al (2019)

Table 2. Outcomes of patients with progressive multifocal leukoencephalopathy treated with immune checkpoint inhibitors (continued)

Nivolumab	53/M	Silicosis	12 weeks	Not detected	No	(++) Stabilised aphasia and regression of motor deficit	Audemard-Verger et al (2019)
Nivolumab	65/F	Hodgkin's lymphoma	0 days	Not detected	Yes	(++) Clinical function improved	Hoang et al (2019)
Nivolumab	81/M	Kidney transplant	<6 weeks	3162	No	(-) Death 6 weeks after diagnosis	Medrano et al (2019)
Nivolumab	77/M	Kidney transplant	<6 weeks	794	No	(-) Death 6 weeks after diagnosis	Medrano et al (2019)
Nivolumab	67/F	Kidney transplant	<6 weeks	794	No	(-) Death 4 weeks after diagnosis	Medrano et al (2019)
Nivolumab	47/F	Acute myeloid leukaemia after allo-stem cell transplantation	4 weeks	47 377	No	(++) Complete recovery from motor deficit. Visual symptoms stabilised	Uzunov et al (2019)
Nivolumab	60/F	Idiopathic primary immunodeficiency	8 weeks	200 000	Yes	(++) Improved focal deficits and alertness	Walter et al (2019)

Key: (–) unfavourable outcome; (+) mild improvement; (++) marked improvement and (=) no change. F = female; IRIS = immune reconstitution inflammatory syndrome; M = male; PML = progressive multifocal leukoencephalopathy.

No side effects from allogeneic T-cell therapy were reported in any patient. The heterogeneity in underlying conditions in this small case series and the use of multiple treatments makes assessing efficacy challenging. The potential use of patient-specific products and/or third-party products may expand the feasibility of this therapy (Fatic et al, 2020).

Filgrastim

Filgrastim (also known as granulocyte colony-stimulating factor) is often used to boost the immune system after chemotherapy. It promotes production of granulocytes, lymphocytes, antigen-presenting cells and improves adhesion of T-cells to the blood vessel wall. These features promote immune system function, potentially enabling an anti-progressive multifocal leukoencephalopathy effect.

Stefoski et al (2019) published a retrospective cohort study of 17 patients treated with filgrastim for natalizumab-induced progressive multifocal leukoencephalopathy. Natalizumab was stopped in all patients after the diagnosis of progressive multifocal leukoencephalopathy. All patients were treated with daily filgrastim until lymphocyte counts doubled. In addition, 8 patients underwent plasma exchange, 14 received mefloquine, 15 received mirtazapine, and 9 were treated with maraviroc. Of the 17 patients, 15 developed immune reconstitution inflammatory syndrome which was treated with intravenous methylprednisolone followed by tapering doses of corticosteroids. Filgrastim was well tolerated, with bone pain not necessitating cessation of treatment the only side effect reported. Outcomes were very good, with all 17 patients surviving 2 years after progressive multifocal leukoencephalopathy onset; survival after natalizumab-induced progressive multifocal leukoencephalopathy has been reported in other cohorts as 76% (Dong-Si et al, 2015). Functional outcomes were mixed, with seven patients improving to baseline that they showed at diagnosis of progressive multifocal leukoencephalopathy, three improving but not to baseline, and seven having poor outcomes (requiring full care). Patients who developed immune activation

Key points

- Progressive multifocal leukoencephalopathy is a devastating disease with poor prognosis, particularly where immunosuppression cannot be reversed.
- Existing treatments are ineffective or unproven.
- Novel treatments for progressive multifocal leukoencephalopathy boost the anti-JC virus immune response via immune checkpoint inhibitors (pembrolizumab and nivolumab), BK-specific T-cell therapy, and filgrastim.
- These treatments have shown benefit in cohort studies, but conclusions are limited by small sample sizes, heterogeneous patient cohorts, and multiple confounding factors.
- Multicentre randomised controlled trials will help establish why treatment appears to be effective in some patients, but less so in others.

after filgrastim and/or immune reconstitution inflammatory syndrome had better clinical outcomes; the authors note that careful timing of steroid treatment for progressive multifocal leukoencephalopathy immune reconstitution inflammatory syndrome is important. Plasma exchange had no effect on outcome. The retrospective nature of the study and the use of multiple drugs means that cause and effect are difficult to establish. The benefit of this study was that it included a homogenous group of patients with multiple sclerosis, allowing more specific conclusions about progressive multifocal leukoencephalopathy in this population to be drawn.

Conclusions

Progressive multifocal leukoencephalopathy is a devastating disease, especially when immunosuppression cannot be reversed. Previous treatments have not been shown to be efficacious in clinical trials. The growing number of patients with iatrogenic immunosuppression is likely to result in a rising incidence of progressive multifocal leukoencephalopathy, highlighting the importance of developing effective therapies for progressive multifocal leukoencephalopathy. Novel treatments for progressive multifocal leukoencephalopathy focus on boosting the anti-JC virus immune response via immune checkpoint inhibitors (pembrolizumab and nivolumab), BK-specific T-cell therapy, and filgrastim, all of which have shown benefit in cohort studies. Limitations of these studies include small sample sizes, heterogeneous patient cohorts and multiple confounding factors. As use of these expensive therapies increases, it may be possible to identify patient factors that predict good response and to develop combinatory treatment modalities. Future studies should test these treatment methods in more specified patient groups, with standardised outcome measures. A multicentre randomised controlled trial would be the best way of showing efficacy, although the rarity of progressive multifocal leukoencephalopathy may make this challenging. Despite the initial promise of these novel treatments it is important to set realistic patient expectations given that many patients remain extremely disabled even after successful treatment of progressive multifocal leukoencephalopathy.

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Conflicts of interest

The authors declare no conflicts of interest.

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