Progressive Multifocal Leukoencephalopathy Therapy

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Abstract

Progressive multifocal leukoencephalopathy (PML) is caused by the JC virus in the setting of chronic immune deficiency. Developing therapy has been challenged by the rarity of the disease as well as the complexity of patients in whom it develops. Several small trials directed at presumptive antiviral therapies have failed to show convincing clinical efficacy. However, the prognosis of PML has evolved from an almost uniformly fatal encephalitis to a disease where a majority of patients survive. This improvement in outlook has been driven by effective immune reconstitution strategies for the underlying disease, most prominently the improved therapy for human immunodeficiency virus and ability to reverse the effects of natalizumab. While a rapid acting and effective antiviral therapy remains a sought for goal, optimal immune reconstitution to control JC virus without causing brain damaging immune reconstitution inflammatory syndrome (IRIS) currently is the most practical approach to treat PML.

Keywords

progressive multifocal leukoencephalopathy; PML; JC virus; natalizumab; IRIS; immune reconstitution inflammatory syndrome

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare viral brain disease caused by replicative JC virus infection of oligodendroglia in the brains of immune compromised

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patients. JC virus, which is a polyoma virus, infects a majority of adults, but does not invade the brain nor cause any disease save when the immune system is compromised. PML is rare, being seen occasionally in the setting of hematologic malignancies, organ transplantation, autoimmune diseases such as systemic lupus erythematosus (SLE) where chronic immune suppression is used. However, prolonged and profound cellular immune deficiency such as develops in advance human immunodeficiency virus (HIV) infection results in many more cases, and has made PML a much more prominent disease.¹ In the past decade, renewed interest in PML has occurred because of the development of PML associated with use of monoclonal antibodies, most prominently the integrin inhibitor natalizumab that has been widely used to treat multiple sclerosis.² Other monoclonals with increased risk include efalizumab³ and rituximab⁴ Given the expanding population at risk for PML, the serious morbidity and mortality of PML and the notable impact this complication has on drug development, effective therapy for PML has become an important research goal.

Antiviral Therapy for JC Virus

Development of antiviral therapy has been challenging due to the absence of an animal model of PML, and the difficulty of studying JC virus in vitro. Isolated case reports have proved highly unreliable measure of potential drug efficacy for PML. Since JC is a DNA virus, previously developed therapies with activity against DNA viruses have been considered. Anecdotal reports and in vitro activity supported cytosine arabinoside as having activity against JC virus.⁵ A randomized trial testing cytosine arabinoside in HIV associated PML failed to demonstrate clinical benefit.⁶ It has been hypothesized this failure derived primarily from inability to deliver the drug to affected areas of the brain either through intravenous or intrathecal administration. Cidofovir was widely employed without any convincing demonstration of activity, then when tested proved to have no measurable benefit.^{7,8} Interferons have also been considered as therapeutics for PML but most evidence points to little efficacy, and the association of natalizumab associated PML in patients on interferon-beta and natalizumab raised concern that interferon might actually augment risk of PML.⁹ While this appears unlikely, there is no good in vivo evidence supporting useful activity of interferons against JC virus. The most recent antiviral therapy seriously tested was mefloquine. This anti-malarial was found to have activity against JC virus in an in vitro high throughput screen of drugs.¹⁰ Given the safety and availability of this drug and urgent need for better therapy for PML, an international randomized trial was organized to test its activity. Accrual was difficult. The majority of HIV associated PML patients recruited had a relatively good outcome most likely due to HIV therapy achieving immune reconstitution. Thus, it was impossible with this sample to demonstrate whether mefloquine had antiviral activity.¹¹ No further antiviral based clinical trials are in progress. Theoretical observations suggested potential activity of serotonin antagonists such as mirtazapine, resulting in widespread use of this drug, without any convincing evidence that it has activity in vivo.^{12,13} In the present environment, improved survival, and frequent prompt response to immune reconstitution makes recruitment of an informative cohort of patients exceedingly difficult. Transplant patients and post chemotherapy patients who have a much worse prognosis and might be more informative regarding drug activity, are a distinct minority of

available PML patients, as well as being a complex clinical study population due to multiple simultaneous medical complications.

Immune Reconstitution as Therapy for PML

PML has been a subacute lethal condition in many of the settings where it is seen, and appropriately acquired a grim reputation. However, the assumption that patients were likely to die of this condition has been modified as it occurs in settings where prompt reversal of immunosuppression is possible. In the setting of HIV, development of combined antiretroviral therapy (cART) remarkably results in very rapid improvement in the immune response. With this intervention, it is now the expectation that a majority of affected patients will survive, albeit with significant neurologic deficits in most cases.¹⁴

Encouraged by this relative success, attention to immune reconstitution or reversing immunosuppression has been a focus of management of PML. It must also be emphasized that early diagnosis is very important to optimal clinical outcome. Since demyelination due to JC replication in oligodendrocytes causes a serious and generally poorly reversible disability, restoring the immune response at the earliest time in the infection is critical. In very high risk patients such as natalizumab treated patients with positive JC virus antibody titers, prior immunosuppressive therapy and two years or more of natalizumab therapy, periodic MRI screening has detected pre-symptomatic PML which has had a much better clinical outcome than has been associated with clinically evident PML.¹⁵

The available methods for immune reconstitution vary by disease setting, but the outcomes have been similarly encouraging in several settings. At present the outlook for PML survival is significantly impacted by the degree and speed with which immune suppression can be reversed. In the setting of organ transplantation, it is often not possible to sacrifice transplants by stopping immune suppression, and outcomes tend to be poor. On the other hand, in natalizumab associated PML, it has been standard practice to perform plasma exchange resulting in rather rapid recovery of integrin function and subsequent restoration of immune surveillance within the brain.¹⁶ Under these circumstances survival occurs in >70% with functional outcomes spanning severe neurologic injury to mild deficit.^{17,18} While it seems rational to achieve immune reconstitution as quickly as possible, there have been no randomized observations to inform how critical speed of reconstitution is to prognosis. Because PML has been demonstrated to kill advanced HIV patients within 3-4 months of symptom onset⁶, it would seem urgent to block ongoing progression of PML as rapidly as possible. In the case of HIV therapy, there is no clear evidence to favor specific cART regimens for speed of immune reconstitution, and comparison of protease or non-nucleoside based regimens has not clearly demonstrated different outcomes for PML patients. A small study using maximally aggressive HIV therapy gave a high rate of survival, but was not controlled.¹⁹ However, concern that overly rapid immune reconstitution might be unfavorable has been a concern.²⁰

Treatment to augment immune reconstitution in hopes that it could further improve prognosis continue to be discussed. They seem most relevant in the rarer cases of PML associated with chronic long acting immune modulators, or where the cellular immune

system cannot be reconstituted in the short term such as in cancer patients, and those with idiopathic CD4 lymphopenia or hematologic malignancy. Discussion of IL-2 as a means to enhance immune response have circulated for some years, but large experiments in HIV patients with IL-2 were disappointing, and no large trials using IL-2 for PML have ever been organized.²¹ More recently, interest in glycosylated recombinant IL-7 immune enhancement for several cases of PML has led to discussions of an international clinical trial of this cytokine.²²

Immune Reconstitution Inflammatory Syndrome (IRIS)

Given that HIV and natalizumab associated PML are the most common causes of PML, limited immune reconstitution may not be the critical obstacle for PML therapy in most cases in 2014. Indeed, it is quite possible that the significant contributor to PML outcomes in the current era is driven by immune reconstitution inflammatory syndrome (IRIS) with development of dangerous excess inflammatory changes. A malignant inflammatory response in the brain (IRIS) can be challenging to distinguish from neurological dysfunction of dying oligodendrocytes driven by continuing JC virus replication. Much evidence now points to a startling transformation of the characteristically bland PML lesion with little cellular inflammation on pathologic exam typifying this disease in severe immunodeficiency, into a markedly inflammatory condition with exuberant infiltration of inflammatory cells including CD8 as well as CD4 and plasma cells in some cases.²³⁻²⁵ The inflammation results in breakdown of the blood brain barrier and appearance of contrast enhancement on MRI scans. It appears that balancing the degree of immune response to PML may be an essential therapeutic goal to optimize outcomes. (Figure 1) The fact that more than 30% of natalizumab associated PML lesions are contrast enhancing, thus differing from classic PML developing with severe immunodeficiency, emphasizes the frequency of IRIS for PML in this setting.¹⁷ After plasma exchange (PLEX), IRIS seems to reliably develop in almost all MS patients with PML. This results in progressive deficits, sometimes leading to death. Given this anticipated and potentially harmful IRIS, the therapeutic challenge is to determine the optimal way to control the immune response such that the JC infection driving PML lesion is quickly arrested, while preventing “immune overshoot” resulting in inflammatory brain damage.

Use of corticosteroids has been the mainstay of therapy to control IRIS, and relatively aggressive use that has been used in management of natalizumab associated PML is associated with the best outcomes overall reported with PML. Observational cohorts similarly suggest that relatively early and aggressive corticosteroid therapy is likely beneficial.²⁶ However, there remain theoretical concerns about risks of enhancing immune suppression in the setting of a life threatening opportunistic infection like PML.²⁷ Thus, most clinicians seek to withhold corticosteroids until a well demonstrated IRIS response is identified, then titrate the inflammatory response as conservatively as possible. However, sometimes the severe and prolonged IRIS response may be dangerously difficult to control once it is underway.

Alternatives to corticosteroids might be beneficial. One interesting approach with some anecdotal evidence is use of the CCR5 chemokine receptor antagonist maraviroc. This drug

was developed as a therapy for HIV and is effective and well tolerated in treating HIV infection. CCR5 is apparently involved in targeting inflammatory responses, and in animal models blocking CCR5 has inhibited encephalitic responses in animal models and in graft versus host disease in humans.^{28,29} Several case reports including both HIV and natalizumab associated PML support the possibility that maraviroc therapy may blunt IRIS in the setting of PML.^{30,31} It appears that a potentially useful randomized trial testing optimal immune reconstitution with or without maraviroc would provide scientifically useful observations. However, complexities in the design and difficulty in recruiting and supporting such a trial have proved challenging. Validation of biomarkers that could reliably measure IRIS more specifically would greatly enhance our ability to titrate therapy for IRIS while optimizing PML outcomes. MRI contrast enhancement is probably the most widely used marker of IRIS. While this is a valued tool when positive, it is likely to be an insensitive marker for IRIS. Pathologically notable IRIS may fail to be associated with MRI contrast enhancement thus underestimating presence of PML IRIS.²⁵ At present, clinical corticosteroid responsiveness is often a surrogate for IRIS, since non-inflammatory PML is not responsive to high dose steroid infusions, while inflammatory PML may show clinical stabilization and improvement time linked to steroid administration. Obviously, this is an unsatisfactory tool to predict the need to treat IRIS.

CONCLUSION

PML continues to challenge clinicians and scientists. It is an important disease, occurs in a wide variety of circumstances, with serious consequences maiming and killing its victims. However, it is still a rare disease, with a rapid time course, making organized clinical trials difficult, and collection of informative cases allowing clear understanding of the full biology of the virus very challenging. Natalizumab associated PML has provided a substantial population at relatively high risk that have been more intensively followed, and this has encouraged useful data collection and monitoring. However, it remains daunting to systematically develop new therapy. At present, optimal care must include speedy immune reconstitution, followed by close management of IRIS that may result in inflammatory neurologic complications. Development of sensitive biomarkers to titrate to an optimal immune response promise to improve outcomes, while encouraging pre-symptomatic or very early diagnosis also can minimize the consequences of this condition.

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Figure 1.

Clinical prognosis for PML is poor when the immune system is deeply suppressed. As the immune response increases (x axis to right), prognosis improves as the JC virus is controlled, but at some point declines once again as pathological immune reconstitution inflammatory syndrome (IRIS) develops. The inset shows marked CD3 infiltration in the brain of a patient with IRIS, that would never be found in PML developing in severely immune compromised hosts. MRI enhancement is absent with absent inflammatory response, but increases as inflammation breaks down the blood brain barrier during immune constitution. Clinical intervention with corticosteroids should shift inflammatory response to the left.