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Clinical Trial Report

Challenges for clinical trials on progressive multifocal leukoencephalopathy

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a disease occurring almost exclusively in immunosuppressed patients. It was extremely rare prior to the advent of human immunodeficiency virus (HIV) infection, but PML has become a major source of morbidity and mortality in that population over the past 2 decades. It has been estimated that as many as 5% of AIDS patients die with PML (Berger *et al*, 1998). Therapy for PML has thus far not been identified, in part because this disease presents unique challenges for the design of clinical trials. As we plan new approaches, it is important to delineate challenges this disease imposes on investigations. Optimal research protocols test an intervention in as homogeneous a research population as possible. Defining the research population is challenged by difficulty in achieving a secure diagnosis for research purposes, varied disease presentations, an unpredictable rate of progression, a variety of situations in which the disease occurs, as well as limitations in the number of cases available for evaluation. It is important to find optimal means of addressing these trial design issues.

Diagnosis of PML has, for years, been challenging. As recently as the mid-1990s, it remained necessary to perform a brain biopsy to ascertain the diagnosis of PML. Although the advent of MR scanning has helped significantly, the presence of typical T2 bright MR images without mass effect and without significant gadolinium contrast enhancement is only partially satisfactory for diagnosis. Fortunately, progress in the use of DNA PCR (polymerase chain reaction) testing on cerebrospinal fluid has afforded a secure diagnosis satisfactory for clinical research. PML is diagnosed when a clinically compatible progressive focal neurologic deficit occurs associated with compatible MR lesions and the presence of JC virus DNA in the cerebrospinal fluid in an immunosuppressed subject. Obviating brain biopsy makes it easier to accrue patients to studies and reduces early morbidity that occasionally results from brain biopsy. It typically speeds the entry of patients into studies because extra time was often required for arranging brain biopsy and achieving histologic evaluation. However, recent reports suggest undiagnosed focal leukoencephalopathies in HIV patients that might be PML but do not have the full pattern of clinical progression, MR lesion, and CSF JC DNA (Antinori *et al*, 2001). It may be that in the HAART era, ongoing evaluation of potential cases of PML that do not meet these diagnostic criteria will require future refinement, potentially still including brain biopsy in many cases. Equivocal diagnoses must be verified with a biopsy of the lesion, a requirement that continues to add to the complexity of accruing subjects to studies.

Clinical presentations vary in this disease, depending on the site(s) of the pathologic demyelination caused by the JC virus. Although the lesions of PML are predominantly localized in white matter tracts, the presentations vary clinically by vast degrees, making common clinical scales to monitor this disease difficult to construct. For example, many patients present with cerebellar lesions and progressive asymmetric ataxia. Scales heavy in motor-performance measures (e.g., EDSS) are sometimes employed. However, visual signs may occur due to posterior hemispheral white matter lesions, whereas lesions undercutting the dominant hemisphere cortex may affect language. Lesions may be relatively silent if they develop in the frontal lobe white matter. The variable clinical presentation has further prompted searching for surrogate quantitative markers for this disease. JC virus DNA levels in the CSF appear likely to provide some measure of disease activity. Falling titers are associated with better prognosis and stabilization of the clinical course (Yiannoutsos *et al*, 1999). Similarly, it makes sense

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that MR lesion volumes will provide a means of following the activity of the disease, but further work to establish the correlation between clinical course and MR lesion is still required.

Disease progression is unpredictable in patients with PML, adding to the challenge of trial design. This may often relate to the level of underlying immunodeficiency. Thus, a means of stratifying by disease-specific immune status would be most helpful but has not yet been achieved. Higher CD4 counts have been associated with a better clinical course (Clifford *et al*, 1999). However, it is not easy to stratify on this marker, particularly as it often changes substantially in response to HIV therapy. It is unfortunately impossible to predict the response of an individual subject's CD4 recovery even with successful control of HIV viral load. In any case, for many years it has been recognized that a minority of PML patients may intrinsically be slow progressors or not progress, whereas the majority of such patients progress at a rapid rate resulting in death in 6 months or less. Some control for the level of immunosuppression may help to decrease the degree of variability of progression, but adjustment of the sample size is required to prevent scattered cases with atypical rates of progression from changing the outcome of a therapeutic trial unrelated to the specific intervention employed.

In the present era, there are several groups of subjects commonly presenting with PML. First, there are patients that are not HIV-infected but have immunosuppression of another etiology (e.g., transplant recipients, patients with hematologic malignancies or autoimmune diseases). In the U.S. clinical experience, HIV dominates the overall experience with this disease and for practical purposes makes clinical treatment evaluations logical in this population. However, given scarce patient resources, consideration of studying non–HIV-related PML remains a consideration of some merit. Within the HIV-treated population, a significant number of subjects present with PML as the AIDS-defining diagnosis. These are individuals who have not received the diagnosis of HIV or have failed to seek treatment until this major complication occurred. These patients often have a brisk response to HIV therapy when it is initiated and may in some cases have a better overall prognosis with PML than HIV therapy–experienced patients. Mixing these subjects with those who have failing HIV therapy may give distinctly different therapeutic responses. The other set of HIV-associated PML tends to occur in treated subjects who are virologically failing their HIV therapy. They generally have limited choices to achieve improvements in HIV control and in their immune status. Alternatively, subjects may be failing because of social and behavioral issues making treatment compliance poor. The prognosis of this group needs to be distinguished from the na¨ve and compliant patients. Thus, PML trials will need to define the treated population and/or to stratify for the anticipated different courses that the patients will undergo with therapy. Recognizing the already rather small cohort of subjects with this disease, such refinements of trial design clearly demand a well-designed multicenter effort.

Limitations in overall numbers of cases have been viewed as a serious impediment to clinical trials for PML. However, in several countries, groups of 20–30 patients per year are routinely available for clinical studies even in the post-HAART era (Clifford *et al*, 1999; De Luca *et al*, 2000; Berenguer *et al*, 2001). By combining these resources, it appears entirely reasonable that clinical trials may be achieved. Sadly, the ongoing incidence of PML, which may increase as HAART fails in many patients, appears to make this issue unlikely to be a limiting factor for clinical trial development.

One of the most troubling features in designing a clinical trial is the extremely aggressive nature of this disease. Untreated PML progresses to death very rapidly. In ACTG 243, where cytosine arabinoside was tested, death occurred after a mean duration of only 12–14 weeks of follow-up (Hall *et al*, 1998). Because immune reconstitution takes up to 6 months and is likely incomplete, the rate of progression of PML exceeds the rate at which potential immune reconstitution can be achieved, leaving a dire need for a direct antiviral therapy for PML. Recent uncontrolled experiences evaluating cidofovir and topotecan reveal that uncontrolled trials will typically provide equivocal answers as to the activity of a therapy (Dupont *et al*, 2001; Marra *et al*, 2001). Consequently, it appears necessary that controlled trials be designed. Some have questioned whether this is appropriate, given the grave nature and rapid progression generally associated with this disease.

Even a controlled trial design allowing for escape to active therapy relatively early could doom a substantial number of subjects to further brain damage or death. Most investigators recognize that with such drugs, there remains a real possibility that more harm than good might come of the therapy; thus, controlled trials appear not only ethical, but desirable. Safety monitoring however, is required to assure that as soon as the therapeutic question is answered that the study be terminated. The complexity of endpoint selection for trials has been further complicated by HAART therapy. Previously, death in the first 6 months was so routine that death was a reasonable endpoint for studies. With successful HAART therapy, although death still is a frequent outcome (Marra *et al*, 2001), reported at around half of subjects in a recently described cohort, the survival of many patients requires alternate endpoints for studies. Selection of optimal clinical scales for measurement of clinical outcome will be a necessary part of future trial design.

It is our hope that stimulation of research concerning JC virus reflected in this journal will result

in new strategies that can be tested in patients. With international cooperation, it should be possible to assess efficacy in this disease through careful design of a clinical trial. The ongoing suffering of patients with PML demands that the search go on for more effective and less toxic therapies for this illness.

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