J. Neurovirol. (2013) 19:311–313
DOI 10.1007/s13365-013-0191-9

EDITORIAL

PML therapy: "It's Déjà vu all over again"

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Received: 9 July 2013 / Accepted: 17 July 2013 / Published online: 3 August 2013

It was 55 years ago that Richardson Jr. et al. first described the disease they named progressive multifocal leukoencephalopathy (PML)(Astrom et al. 1958). The emergence of the HIV epidemic catapulted this once rare disease to prominence. The introduction of highly active antiretroviral therapy (HAART) has resulted in a 60–75 % reduction in the incidence of PML (to ~0.6–1.3 cases/1,000 person years of HIV) (Engsig et al. 2009; Khanna et al. 2009); although HIV infection still accounts for ~85 % of all PML cases (Brew et al. 2010). In 2005, the first cases of PML associated with biological immunomodulatory therapy were reported, initially with natalizumab and subsequently, in association with other agents including efalizumab, rituximab, and alemtuzumab (reviewed in Major 2010). There have now been (as of 6 May, 2013) 359 reported cases of natalizumab-associated PML among approximately 115,365 treated patients (as of 31March, 2013), with the risk ranging from <0.1/1,000 in JC virus (JCV) seronegative individuals to 11.2/1,000 in JCV seropositive individuals with prior immunosuppressive therapy who have received more than 24 months of natalizumab treatment. (https://medinfo.biogenidec.com 20 June 2013).

Although isolation of the JC polyomavirus and its identification as the causal agent of PML was reported in 1971 (Padgett et al. 1971), the first use of antiviral therapy in PML was not until 1974 with cytarabine (Ara-C) (Conomy et al. 1974). This agent was later shown to be ineffective in an open-label randomized multicenter clinical trial in HIV-PML which compared antiretroviral therapy combined with intravenous or intrathecal Ara-C to antiretroviral therapy alone (Hall et al. 1998). Another nucleoside analog, cidofovir, was first tested in PML in 1998 (Taoufik et al. 1998). Although a randomized controlled clinical trial of cidofovir in PML has not been performed, a meta-analysis reviewing outcomes from one prospective and five cohort studies failed to identify a survival benefit in HIV-PML (De Luca et al. 2008). One non-randomized and uncontrolled open-label observational study suggested that interferon-alpha could delay progression, reduce symptoms, and prolong survival in HIV-PML (Huang et al. 1998), although a more recent retrospective analysis failed to demonstrate any benefit of interferon-alpha treatment beyond that conferred by HAART alone in HIV-PML (Geschwind et al. 2001). Topotecan, a semisynthetic analog of camptothecan and a topoisomerase inhibitor, was evaluated in a small (11 subject) uncontrolled and un-blinded trial in HIV-PML (Royal et al. 2003). Although 3 of the 11 evaluable patients responded to therapy, the lack of controls and the small sample size precludes any meaningful conclusions, and moderately severe or severe neutropenia, anemia, and thrombocytopenia was seen in 42–83 % of those treated. Other agents tested in PML in mostly anecdotal reports have included interleukin-2 (IL-2) and 5-HT2-receptor antagonists. Enthusiasm for the testing of 5-HT2 antagonists, which include mirtazapine and risperidone, was engendered by initial reports suggesting that the 5-HT2a serotonin receptor could serve as a JCV receptor (Elphick et al. 2004). Subsequent studies suggest that although the 5-HT2 receptor may play a role in JCV cell entry, it is not a JCV cell surface receptor and that the virus, instead, binds to sialylated oligosaccharides that contain a specific pentasaccharide motif ("LsTc") on host glycoproteins (Neu et al. 2010). No controlled trials of 5-HT2 antagonists in PML have been performed, although no noticeable effect on survival was noted in one prospective study of determinants of survival in PML (Marzocchetti et al. 2009), although the number of treated patients was small (9 HIV-PML and 8 non-HIV-PML).

In this issue of the *Journal of Neurovirology*, Clifford et al. (Clifford et al. 2013) report yet another unsuccessful therapeutic trial in PML, this time with the anti-malarial drug

The quoted expression in the article title is attributed to Yogi Berra.

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mefloquine. Mefloquine, like many of its predecessors, was selected for study after a large scale screening of available drugs indicated it could inhibit JCV infection in glial cell cultures, had minimal cell toxicity, and was CNS bioavailable after oral administration (Brickelmaier et al. 2009). The authors are to be commended for the speed in which their open-label rater-blinded randomized treatment trial was performed. Successful and timely completion of treatment trials for viral CNS infection has become a rarity as exemplified by recent failures to report results or continue studies due to poor enrollment issues in WNV neuro-invasive disease (see NCT00068055 and NCT00927953 at clinicaltrials.gov) and the 11 years it took to complete a recently reported trial of long-term oral acyclovir suppressive therapy following standard intravenous therapy in pediatric HSV encephalitis (Kimberlin et al. 2011). Unfortunately, there was no benefit seen in the mefloquine PML trial on any outcome measure including CSF viral load, neuroimaging, clinical efficacy measures, survival duration, or mortality.

The litany of failure in PML treatment trials (reviewed in Hernandez et al. 2009) begs the question of what are we doing wrong. It seems apparent that screening candidate drugs for their ability to inhibit JCV infection in cultured cells, including primary human fetal or transformed human glial cells, is simply an unreliable predictor of the likelihood of subsequent human clinical efficacy. It remains to be seen whether utilization of different JCV strains and improved cell culture models can improve the dismal predictive value of in vitro studies as performed to date. In most models of antiviral drug development, in vitro screening is simply an initial step, which is then followed by testing of promising compounds in experimental animal models of the target human disease. Unfortunately, there is currently no animal model for PML, and none of the available animal models of polyoma virus infection produce a PML-like illness. Finding a suitable animal model of JCV PML would dramatically advance our ability to investigate disease pathogenesis and to screen and evaluate potential treatments.

In contrast to the dearth of efficacious antiviral therapies for PML is the clear recognition that the best protection against the disease is a fully functional immune system, and the associated observation that interventions that lead to immune restoration or reconstitution of host immunity remain the best existing treatment for PML. This message became clear with the advent of HAART and the dramatic impact this had on outcome in HIV-PML (Clifford et al. 1999). It is likely the ability to rapidly restore immunocompetency through accelerated removal of natalizumab by plasma exchange or immunoadsorption that accounts for the remarkably low mortality rate (~22 %) (https://medinfo.biogenidec.com, 20 June 2013) reported to date in natalizumab-associated PML cases when compared to 1-year mortality rates in organ transport recipients (84 %) (Mateen et al. 2011) and even in HAART-treated HIV patients (48 %) (Marzocchetti et al. 2009). Virtually, all patients who develop PML following exposure to biological immunomodulatory agents such as natalizumab will also subsequently develop JCV immune reconstitution inflammatory syndrome (IRIS) after drug cessation and accelerated removal (Tan et al. 2011) Understanding how to modulate the adverse effects of IRIS-associated immune-mediated CNS tissue injury without impeding the beneficial effects of immune-mediated JCV clearance will hopefully lead to further reduction in PML morbidity and mortality. To date, treatment regimens for PML-IRIS are empirically driven rather than based on data from controlled clinical trials (Dahlhaus et al. 2013), and this situation needs to be remedied to ensure that therapy is driven by science rather than guesswork.

Disclosures Dr. Tyler has served as an expert consultant related to JC virus and PML for the PML Consortium, Biogen Idec, Genentech, Janssen Pharmaceuticals (Johnson & Johnson), Pfizer, and Roche.

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