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Review Article

Polyomavirus-Associated Progressive Multifocal Leukoencephalopathy (PML) in HAART era

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ABSTRACT

Polyomaviruses may cause human disease, particularly in immunocompromised hosts. JCV, one of the members of polyomaviridae family, is the causative agent of the neurological disease progressive multifocal leukoencephalopathy (PML), which occurs mostly in immunocompromised patients. Progressive Multifocal leukoencephalopathy (PML) is a progressive demyelinating disorder of the central nervous system (CNS) resulting from infection of oligodendrocytes by JC polyomavirus. Whereas after highly active antiretroviral therapy (HAART), the incidence of nearly all of all neurological complication have decreased, this article evaluates the incidence and prognosis of JC polyomavirus-associated PML including a unchangeable incidence of PML associated with JC polyomavirus compared with other opportunistic disease and paradoxical results of disease remission in HAART era.

Keywords: Polyomavirus, JCV, PML, HAART, Epidemiology

INTRODUCTION

Human Polyomaviruses. Previously, JCV and BKV were the only polyomaviruses considered as human pathogens. Today, the human polyomavirus family has been expanded to 10 members including JCV, BKV, KIPyV, WUPyV, MCPyV, HPyV6, HPyV7, TSPyV, HPyV9 and MWPyV. Serological studies suggest that human polyomaviruses infect the general population. KIPyV and WUPyV have been found in the respiratory tract (Allander et al., 2007; Gaynor et al., 2007; Abedi Kiasari et al., 2008), MWPyV in stool and skin, HPyV6, HPyV7, and HPyV9 in serum and skin. However, the pathogenicity and the clinical significance of these newly described human polyomaviruses remains speculative. TSPyV was identified in a rare skin disease (trichodysplasia spinulosa). MCPyV has been associated with a rare skin cancer, Merkel cell carcinoma (MCV) and isolated from respiratory tract, blood and skin (Messam et al., 2003; Feng et al., 2008; Goh et al., 2009; Abedi Kiasari et al., 2011). Similar to MCPyV, SV40 a monkey polyomavirus was shown to be oncogenic and could induce tumors in human and be invoved in kidney transplantation failure (Lednicky et al., 1997; Abedi Kiasari et al., 2011). Both JCV and BKV may cause human disease, particularly in immunocompromised hosts such as patients with AIDS or transplant recipients. BKV-associated disease includes haemorrhagic cystitis,

ureteric stenosis and nephropathy which occurs mainly in transplantation patients (Hirsch and Steiger, 2003). JCV is the causative agent of the neurological disease progressive multifocal leukoencephalopathy (PML), which occurs mostly in AIDS affected patients (Major et al., 1992).

Progressive Multifocal Leukoencephalopathy (PML). In 1958, Astrom et al. (1958) described an unusual neuropathologic disorder in patients with lymphoma and leukemia. Each patient presented with progressive dementia, dysphasia, and pyramidal tract involvement. Also, they identified five other cases in the literature dating back to 1930: in these cases, associated systemic illnesses included sarcoidosis and tuberculosis. The patients had progressive dementia, motor dysfunction, and vision loss with death occurring within months. An opportunistic viral infection was suggested as a cause of the disease. Compiling these observations and citing the apparent uniqueness of this disorder, the illness was termed progressive multifocal leukoencephalopathy (PML). PML is a progressive demyelinating disorder of the central nervous system (CNS) resulting from infection of oligodendrocytes by JC polyomavirus. Before the AIDS epidemic, PML was a rare opportunistic event, occurring most commonly in the setting of cellular immune deficiency. However, PML has become an increasingly common neurological complication in the developed world. Drug-induced immunosuppressions, occurring in transplant recipients or patients with autoimmune disease, have contributed to the increasing occurrence of PML. At the time of initial description of PML, the aetiology of the disorder remained uncertain. In 1965, Zu Rhein and Chou (1965) used electron microscopy to describe papovavirus-like crystalline arrays in the nuclei of oligodendrocytes from patients with PML. Subsequently, PML was defined as having a viral aetiology when a unique human fetal glial cell cultures inoculated with brain extracts from PML patients (Padgett et al., 1971) were shown to become infected with the viruses. It was named JCV after the person from whom it was isolated. To date JCV appears to be the only virus responsible for the disorder. PML presents as an insidious, sub acute disease and indications of infectious inflammatory disease are often minor or absent. In a review of 69 pathologically confirmed and 40 virologically and pathologically confirmed cases of non-AIDS- associated PML, neurological signs and symptoms of PML were studied by Brooks and Walker (Brooks and Walker, 1984) This study revealed that visual deficit was the most common presenting sign, present in 35 to 45% of cases. Among these cases, homonymous hemianopsia (loss of vision for one- half the visual field in each eye) was the most common. At the time of diagnosis 6 to 8% of the patients were cortically blind, in 25 to 33% of cases; motor weakness was the initial sign. Hemiparesis or hemiplegia was the present in nearly all patients. A change in mentation was the presenting sign in approximately one-third of cases and eventually involved most patients. Therefore, the clinical features of PML, depends on the location of the lesions in the CNS, including visual impairment or blindness, motor dysfunction or weakness, dementia, cognitive impairment, cranial nerve palsies and other cognitive abnormalities, such as personality change, memory loss, or emotional lability (Major et al., 1992). PML lesions can even mimic a cortical disorder. For example, areas of demyelination underlying the language centres in the left frontal and temporal lobes will result in aphasia, and lesions in the occipital white matter can be indistinguishable from cortical blindness. In terms of presentation and severity, these clinical features can vary. However, most patients develop all them. Vertigo, headache, seizures, sensory deficits, and Parkinsonism are less common features in these patients. Seizures, which are usually thought to be a manifestation of cortical injury rather than of white matter disease occur in up to 18% of patients with PML and have been associated with white matter lesions immediately adjacent to the cortex (Lima et al., 2006). With seizures, the disease progression is usually rapid and the patient is severely disabled eventually becoming demented, blind and paralysed. Death occur

usually less than a year after diagnosis. Also, some patients survive with PML for several years (Kepes et al., 1975). While PML occurs in immune-suppressed individuals, the underlying immunosuppressive disorder or treatment does not alter presently symptoms (Sabath and Major, 2002). PML occasionally results as a consequence of primary infection in an immunosuppressed person. However it has been suggested that most cases of PML appear to result from reactivation of a latent or persistent infection during a decline in immune status. The first is observed in very young children with innate immune deficiencies. The later hypothesis is supported by the finding of JC virus in the urine of pregnant women and persons who have undergone organ transplantation, as well as PML patients. Immunodeficiency is associated with all of these cases (Dorries, 1984). The following series of events might occur in a reactivation case of PML. After an initial exposure, the virus must establish latency. Studies of antibody to JCV in patients with PML indicate IgG rather than IgM implying that the disease results from a reactivation of a latent infection (Weber et al., 2001). It is thought that if the virus were to be reactivated all seropositive individuals support JCV latency at a site that would lead to brain infection. For instance, the virus genotype that establishes latency in kidney (the archetype) cannot support replication in glial cells indicating that this site of latency may not distribute in the pathogenesis of PML. Alternately, JCV isolates from bone marrow, spleen, and tonsillar tissues can replicate in brain tissues suggesting that this site may have a role in the pathogenesis of PML (Berger and Houff, 2006). JCV may be reactivated from a latent state within the brain. The ability of JCV to replicate in neuroglial cells suggests that brain might be a site of virus latency. In support for this hypothesis, some studies using sensitive PCR have demonstrated asymptomatic infection of JC virus of the brain in patients without PML (Aksamit, 1995). JC virus can reactivated from a non-CNS organ and disseminate to the brain at the time of immunosuppression. This has led investigators to speculate that JC virus is disseminated by a haematogenous rout at the time of immunosuppression to the brain via lymphocytes. It is suggested that the multifocal distribution of distinct foci of demyelination in PML follows haematogenous spread of the virus to the brain. JCV genome exists in the B-Lymphocytes of normal persons who have been infected with JCV (Shah, 1996). It has been suggested that during the course of multiplication in the immunocompromised host, JCV-infected B-Lymphocytes could gain access to glial cells since activated lymphocytes do not require antigen-specific recognition to cross the blood-brain barrier (Major et al., 1992). In deed, two CD34+ haematopoietic progenitor cell lines (KG-1 and KG-a) as well as primary CD34+ haematopoietic progenitor cells isolated from human fetal liver did demonstrate evidence of infection following JC virus exposure (Monaco et al., 1996). Thus, JCV may traffic to the brain via infected B cells (Monaco et al., 1996; Monaco et al., 1998). JCV has also been occasionally detected in the brain vascular endothelial cells of PML patients (von Einsiedel et al., 2004). The importance of JCV infection of lymphocytes in the pathogenesis of PML has been emphasized by recent reports of PML in patients receiving natalizumab for multiple sclerosis and Grohn`s disease (Kleinschmidt-DeMasters and Tyler, 2005; Van Assche et al., 2005; Yousry et al., 2006). Natalizumab is an m Ab against adhesion molecules known as very late antigen 4 (VLA-4). It works by interfering with the process that pulls white blood cells into the CNS from the blood, gets them across the blood- brain barrier. In fact, it is the white blood cells believed to mediate the damage in multiple sclerosis. While decreased T-cytotoxic cell responses to JCV infection had a role in the pathogenesis of PML in these patients, mobilization of JCV infected B-lymphocytes from the spleen and bone marrow may have provided the source of JCV that led to neuroglial cell infection and PML (Ransohoff, 2005). Although JCV can infect both astrocytes and oligodendrocytes, productive infection is established in oligodendrocytes, and these cells are predominantly destroyed by the

virus. In the CNS with PML, the key pathogenetic event is the cytocidal infection of oligodendrocytes with JCV replication resulting in the loss of myelin. It causes severe deterioration of brain function. Initially focal lesions of demyelination develop in one region of the brain, but during advanced stages of PML, they may also be observed in other regions. This results from migration of JCV from the original area of demyelination (Yogo et al., 2001). Even though lytic infection occurs in oligodendrocytes, there is evidence of infected astrocytes *in vivo*; raising the possibility of astrocytic involvement in the spread of infection to neighbouring cells (Aksamit, 1995). Of interest, human brain derived progenitor cells can also support JCV infection (Messam et al., 2003). JCV can infect primary progenitor and progenitor derived astrocytes. Therefore, progenitor and some progenitor derived cells of both the immune and nervous system may play roles in JCV pathogenesis and the development of PML. Alteration in DNA repair pathway may be important for the pathogenesis of PML. In a study, the occurrence of DNA damage, chromosome instability, and change in the DNA repair during the course of JCV infection of astrocytes and oligodandrocytes has been examined. This study suggested that JCV infection induce chromosomal instability and DNA damage by the occurrence of increased ploidy in metaphase spreads with time of infection (Darbinyan et al., 2007).

In AIDS era, it has been believed that patients with AIDS developed PML. There are multiple reasons for the high incidence of PML in HIV patients. JCV infection of 5HT2AR expressing cells such as vascular endothelial cells, astrocytes and choroid plexus cells play an important role in the pathogenesis of PML. It is possible that 5HT2AR receptor expression is low in normal brain but higher in the brain of patients infected with HIV explaining their susceptibility to PML. The relatively incidence of PML in HIV-infected patients may be related to the profound depression of T-cell function in this group (Malhotra and Sidhu, 2006). HIV-1 infected cells are capable of secreting viral regulatory proteins, including the HIV-1 transactivation protein, Tat (Frankel and Pabo, 1988; Ensoli et al., 1990). Tat, an HIV-encoded trans-regulatory protein has been shown to increase the basal activity of JCV late promoter in glial cells. Tat may enter cells and target dormant JCV for activation. Moreover, indirectly Tat through cytokines may participate in de-regulation of cellular and activation of the viral promoter in neuronal cells in CNS. Cytokines can originate from resident cell of the nervous system specifically astrocytes and microglia cells or from cells of the immune system that traffic through the CNS (Persidsky et al., 1999). Several cytokines, such as TNF, Interleukin1 (IL-1) and transforming growth factor β (TGF β) may contribute to the pathogenesis of the neurological disorders of HIV infection (Genis et al., 1992) IL-1β has been demonstrated to rapidly increase JCV transcription in glial cells by inducing nuclear factor-1 binding to the JCV enhancer region, increasing transcriptional activity of the viral early promoter. Transforming growth factor-β1, by stimulating downstream factors, has been shown to augment transcription of the JCV promoter in glial cells (Berger and Houff, 2006). To further study of the relationship between HIV and the development of PML, Manley et al. (2006) examined the link between the expression of inflammatory cytokines and JCV infection by testing an anti-inflammatory compound, Cyclosporin A (CsA), for its ability to block JCV infection of glial cells. They found that CsA inhibited JCV infection by preventing the activation of the transcription factor nuclear factor of activated T cell 4 (NFAT4). Due to increasing levels of TNF-a and IL-2 which are strong activation of calcium signalling, activation of NFAT4 in HIV-infected patients may be directive for JCV infection of the CNS. NFAT4 directly bind to a site in the JCV promoter region and activate early and late viral transcription. This study suggested that calcium signalling and the activation of nuclear factor activated T cell in glial cells are necessary for JCV infection of the CNS. Gasnault et al. (2003) reported that loss of JCV specific CD+4 cytotoxic lymphocytes in AIDS patients has also been correlated to the development of

PML in HIV patients. In PML, pathological alterations are seen in the cerebrum, cerebellum, or brain stem. Although cerebral cortex and deep gray matter are normal, lesions are evident in areas of retraction within sub cortical or deep white matter (Seth et al., 2003). This results from the lytic infection of myelin-producing oligodendrocytes by JC virus. Microscopic areas of necrosis can become macroscopic plaque lesions that range in size from 1mm to several centimetres in diameter (Sabath and Major, 2002). Virion is less frequently detected in astrocytes than in oligodendrocytes, and neuronal loss is rare, with sparing of demyelinated axons (Ledoux et al., 1989). Recently, some studies reported a lytic infection of cerebellar granule cell neurons by JCV in a human immunodeficiency virus (HIV)-infected patients with PML. This neuronal infection resulted in focal loss of granule cell neurons leading to cerebellar atrophy (Tyler, 2003). Inflammatory infiltrates are also seen in patients with PML. The course of PML tend to be protected when lymphocytic perivascular cuffing and paranchymal accumulation are revealed (Major et al., 1992). Highly active antiretroviral therapy affects on immune recovery and result in immune reconstitution in patients infected with human immunodeficiency virus (HIV). HAART can improve the survival time in these patients and decrease morbidity and mortality (Dyrhol-Riise et al., 2001). HAART is currently used for a combination of three or four anti- HIV drugs from the following classes-nucleoside, revers transcriptse inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. Prior to the AIDS era, malignant proliferative diseases were the dominant basic disorder PML in about half of cases (Dorries, 2004). Currently, because AIDS accounts for most of PML cases, it is not surprising that antiretroviral therapies have been extensively used to treat AIDS-associated PML (Seth et al., 2003).

Epidemiology. It was estimated that 39-70% of all patients with AIDS or symptomatic HIV infection developed neurological complication. However, after introduction of highly active antiretroviral therapy (HAART) several studies suggested that the incidence of CNS-defining disease such as toxoplasmosis, primary brain lymphomas, AIDS dementia complex (ADC), cryptococcal meningitis and HIV encephalitis has been reduced (Ledergerber et al., 1999; Jellinger et al., 2000; Masliah et al., 2000; Stankoff et al., 2001; Sacktor et al., 2002; d'Arminio Monforte et al., 2009). The results of a study by d'Arminio Monforte et al. (2004) on HIV-infected individuals from 1994 to 2002 showed that the incidence of AIDS-defining CNS disease has decreased. A decline in the incidence of CNS-disorders has been observed in very recent years. UK collaborative HIV cohort (CHIC) study steering committe reported that incidence of all CNS-D declined from 13.1 per 1000 PY in 1996/1997 to 1.0 per 1000 PY in 2006/2007 (p=0.0001) suggesting an ongoing decline in the incidence of CNS-D (Garvey et al., 2011). In the past 2 decades and before the HAART therapy, AIDS has led to a dramatical incidence in PML. The reported prevalence of PML in AIDS patients varies between 0.7 and 8% (Krupp et al., 1985; Petito et al., 1986; Holman et al., 1991; Berger and Concha, 1995; Martinez et al., 1995; Berger, 2000). Although the incidence of nearly all of AIDS associated opportunistic disorder of the central nervous system (CNS) such as toxoplasmosis, cryptococcosis, primary cerebral lymphomas and CMV encephalitis have decreased, the incidence of PML has not significantly decreased in the era of highly active antiretroviral therapy (HAART) (Berger and Major, 1999; Antinori et al., 2001). Whereas, PML has shown 0.72% prevalence among persons with AIDS reported to CDC from 1981 to June 1990 (Holman et al., 1991), a CDC review of 415 cases of PML from 1990 to 1997 in united states showed that the prevalence of PML among 45,398 persons with AIDS who had died (15,246 patients) was 2.4% (Dworkin et al., 1999) suggesting the prevalence of PML from 1981 to 1997 has increased. Gray et al. (2003) analysed 343 brains with AIDS from patients who died between 1996 and 2002. Since HAART has been available for AIDS patients in France from 1996, they studied change in

the pattern of HIV in 23 patients had died between 1997 and 2002. Despite, French's researchers found an overall decreased in incidence of neurological disorders, the incidence of PML remained stable. Antinori et al. (2001) demonstrated that between the pre-HAART and the HAART period, although the prevalence of AIDS-related neurological disorder has reduced, PML incidence has not significantly decreased. In a study, between January 2000 and June 2002, prevalence of PML among 714 neurologic patients registered in Italian registry investigative neuro AIDS (IRINA) was analysed. In this study, PML shows a 14.1% prevalence (101 cases) suggesting even HAART era, the incidence of PML did not significantly differ (Antinori et al., 2003). Engsig et al. (2009) reported an incidence of 3.3, 1.8 and 1.3 PML cases per 1000 person- years at risk in 1995-1996, 1997-1999 and 2000-2006 respectively suggesting that the incidence of PML in HIV-infected patients decreased after the introduction of HAART. A study in Japan, investigated trends in neurological complication of infection with HIV immediately after introduction of HAART (1999-2001) and a few years later (2002-3). Although prevalence of some of the neurological complication such as HIV encephalopathy decreased markedly over the study period, prevalence of PML did not decrease (Yoritaka et al., 2007). In contrast to studies reported no decline in the incidence of PML among patients treated with HAART, some recent studies reported that the incidence of PML decreased after HAART therapy. Casado et al. (2014) reported that the incidence of PML decreased from 14.8 cases/1,000 patients/year in 1996 to 2.6 in 2005 and 0.8 in 2011, and nearly two-thirds of recent cases (64 %) were observed in HIV patients not attending clinical visits.

Survival Time. Before the introduction of highly active antiretroviral therapy (HAART), the survival times of people with PML was 4-6 month (Berger and Mucke, 1988; Berger and Major, 1999) and was associated with a rapidly fetal outcome. In recent years, several studies demonstrated a prolonged survival in AIDS- associated PML with HAART therapy. (Dworkin et al., 1999) described that protease inhibitor use (in combination antiretroviral therapy) was the most likely factor to improve survival time after diagnosis of PML. They found a significant reduction in the risk for death with PML associated with prescription of combination antiretroviral therapy suggesting these medication influences on the prognosis of PML. Study of IRINA showed that survival time among people with PML using HAART was higher 1-year compared without using HAART suggesting the use of HAART significantly improved survival time, although prognosis HIV-infected patient with PML is still sever (Antinori et al., 2003). Also Antinori et al. (2001) reported that in the HAART era the survival time of people with PML was average 245 days and people with PML survived an average 66 days when HAART was not available. However, they suggested that despite the survival benefit, AIDS-associated PML still has a serious prognosis. Albrecht et al. (1998) analysed the influence of different antiretroviral therapies on the AIDS-associated progressive multifocal leukoencephalopathy (PML) patients admitted to hospital between 1988 and 1996. This study found that a group of people with PML who received a HAART regimen have survival time of grater than 500 days, in comparison with people treated with nucleoside analogues alone (127 days) and people without anti-HIV therapy (123days). They suggested that HAART may improve survival in PML patients. De Luca et al. (1998) reported two observational studies of HIV-positive patients with PML treated with HAART alone and treated with HAART and cidofovir. They suggested that patients in the cidofovir and HAART treatment group survived significantly longer than those in the HAART only group. Inui et al. (1999) reported AIDS-associated PML in a 12 year old child with hemophilia B. They observed an increase of CD4 count with highly active antiretroviral therapy. Patients survived more than 1 year without specific therapy against JCV suggesting HAART appear a remission of PML. A study on 12 patients with AISD-associated

PML indicates that average survival time after diagnosis was 545 days with use of HAART and 60 days in control group. It was suggested that AIDS patients with PML may benefit from HAART therapy and PML is no longer an ultimately fatal disease (Miralles et al., 1998). A study in Spain compared people with PML on antiretroviral therapy and those on no antiretroviral therapy treatment. This study found that first group had 21.9 month survival time and the second group had an average of 2 month survival times (Asensi et al., 1999). Spanish researches reported in approximately one- half of the survivors, neurology function improved. Clifford et al. (1999) found that patients with PML survived 43 weeks with HAART comparison with control group that survival 11 weeks recommending HAART for patients with AIDS and PML. A French study of 31 patients with PML treated with HAART indicated that survival time of this group increased (Tassie et al., 1999). French researchers in another study by comparison with 109 patients with AISD associated PML before the introduction of protease inhibitors and 137 patients after using protease inhibitors found that the risk of death among patients 63% was reduced 6 months after diagnosis (Gasnault et al., 1999). In a large study in 25 patients with AIDS associated PML, Clifford et al. (1999) reported that the median survival time in the first group was 46.4 weeks compared with 11 weeks in the control group. Also, in a large study in 11 hospitals throughout Spain, Berenguer et al. (2003) analyzed survival rates, neurologic function, and prognostic factors for 118 AIDS-associated progressive multifocal leukoencephalopathy treated with highly active antiretroviral therapy (HAART). They reported that 63.6% patients survived for an average 114 weeks (2.2 years). In addition, they demonstrated that one-third of patients with PML died despite receiving HAART. There are other studies showed that HAART has extended the survival time of AIDS-associated PML patients (Berger and Mucke, 1988; Gillespie et al., 1991; Fong et al., 1995; Berger, 2000; Giudici et al., 2000). Christensen et al. (2010) evaluated the rate of PML-associated death rates during 1979-2005. The study revealed that the PML-associated death rates decreased from 2.76 deaths per 1 million persons in 1992-1995 to 0.66 in 2002-2005. They showed that the proportion of HIV-associated deaths from PML decreased between 1992-1995 and 2002-2005 from 1.4% to 1.0%. The study suggested that this decline may reflect increases survival time among HIV positive persons who receive HAART. To evaluate the impact of HAART on the MR pattern of PML in HIV-infected patients, Giancola et al. (2008) reviewed MR imaging at baseline and at the last available follow-up within 6 months of diagnosis of 31 HIV-positive patients affected by PML. The results of study suggest that although HAART prolonged the survival of patients with AIDS-associated PML, it may not influence the PML MR pattern of presentation. Lima et al. (2010) described 24 PML patients (1 HIV negative, 23 HIV positive) whose survival exceeded 5 years (mean: 94.2 months; range 60-188 months). They reported marked neurological improvement, partial improvement and stability in 17%, 46% and 37% of patients. An increased survival times with better prognoses in the patients under HAART has been reported (Cedeno-Laurent et al., 2011). In this report the main differences between PML before and after the HAART era including the new patterns of presentation, the neurotropism of other human polyomaviruses, and the increased prevalence of immune reconstitution inflammatory syndrome (IRIS) have been described. A 43-year-old Caucasian homosexual man with AIDS associated PML, was treated with a combination antiretroviral therapy. Although the median survival of patients with PML was poor before the antiretroviral therapy era, the patient is still alive 12 years after the diagnosis suggesting remission of PML following HAART (Yoganathan et al., 2012). In contrast to studies reported a longer survival rate among patients treated with HAART, some recent studies reported that HAART therapy do not improve the survival time of PML patients and even may present a negative impact on patients. There are studies indicating not significant

benefit using HAART for patients with PML conducted by (De Luca et al., 1998; Gasnault et al., 1999). In a study conducted by Miralles et al. (2001), a total of 28 HIV-infected patients with PML have been treated with HAART. In 3 out of 28 patients (10.7%) clinical and radiological deterioration of PML attributable to inflammatory reaction were observed. In addition, review of 28 slides of brain biopsies diagnostic of PML showed inflammatory change in 4 out of 9 patients on HAART and in 1 out of 19 patients not on HAART. This study suggested a limitation success using HAART in AIDS-associated PML supported by other reports. A Spanish study reported two cases of AIDS-associated PML whose course worsened on HAART therapy (Portilla et al., 2000). Safdar et al. (2002) described 2 patients with AIDS-associated PML that worsened clinically after HAART. They recognized immune restoration disease (IRD) soon after started receiving active antiretroviral therapy. It was thought that despite the use of HAART, PML may remain unaltered in some patients. In the last decade, a new form of PML has emerged in some patients who show new onset or worsening of PML shortly after initiation of HAART (Gray et al., 2005; Martinez et al., 2006). This clinical features occur in the setting of a recovery of the immune system and is associated with an inflammatory reaction in brain lesions (Di Giambenedetto et al., 2004; Vendrely et al., 2005). Falco et al. (2008) analyzed the incidence and survival of HIV-1-infected patients with PML and described the PML-associated immune reconstitution inflammatory syndrome (IRIS). They described a mean of 15 months survival time for PML patients and 14 (23%) cases of PML-associated immune reconstitution inflammatory syndrome (IRIS). The study suggests that despite a higher survival time in patients receiving HAART, PML continues to be one of deadliest infection in AIDS patients. In a study, 35 cases of PML were studied. After diagnosis, all patients take antiretroviral therapy. In 12 patients who were treated by cidofovir and HAART, survival time was significantly shorter than without cidofovir. Also, people with PML who received HAART showed a trend toward a shorter survival than HAART- naïve patients. Therapy with HAART and cidofovir do not improve the survival time of PML patients (Wyen et al., 2004). The combination of HAART and cidofovir showed no significant increase in survival suggesting no benefit for cidofovir in addition to HAART in the treatment of PML in HIV-infected patients (Keramer et al., 2008).

Conclusion

While, after highly active antiretroviral therapy (HAART) the incidence of nearly all of AIDS-associated neurological disorders have decreased, the incidence of PML has not significantly decreased between the pre-HAART and the HAART era. In addition, despite HAART may increase the survival time of AIDS-associated PML, in some patients the prognosis of PML remain stable and even a paradoxical worsening is presented. In fact, PML has poor prognosis and the effect of HAART on the PML is still questioned. AIDS-associated PML still is a serious neurological disorder and continues to occur in the age of HAART and probably requires a specific treatment.

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