Cidofovir in combination with HAART and survival in AIDS-associated progressive multifocal leukoencephalopathy

Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) caused by a human polyomavirus called JC virus. Infection with the JC virus is worldwide and common (about 70% - 85% of all populations studied) and leads to lifelong asymptomatic persistence until an impaired cell-mediated immunity occurs [4, 11, 28, 29]. Before the AIDS pandemic, this was most often due to chronic lymphocytic leukaemia, lymphoma, or other neoplasms. Now, PML occurs mostly (in about 85%) in HIV-infected patients. Up to 5% of all patients with HIV develop a PML [4, 14, 18, 26, 28, 29]. PML is characterized by disseminated demyelinating lesions in the white matter of the CNS, most common in the frontal, parietal, and occipital lobes [4, 26, 29]. Clinically, progressive neurological deficits occur, frequently paresis, gait disturbance, speech or language disorders, and cognitive dysfunction [14, 15, 26, 29]. The diagnosis of PML is based on a characteristic progression of central symptoms, on the
demonstration was defined as p < 0.05. Comparisons in survival by using the log-rank test. Statistical significance of the Kaplan-Meier estimates and the different therapy groups were estimated using the first HIV diagnosis to PML diagnosis was 53.6 months (range 0 to 183). The mean CD4+ cell count was 95/μl (range 7 to 514), all but three patients had a CD4+ cell count less than 200/μl. Mean plasma HIV viral load – obtained in 16 patients (determination of viral load was not possible before 1996) – was 254,000 copies/ml (range 50 to 1,100,000). For 23 patients (69.7%), PML was the first AIDS-defining disease. The HIV infection occurred through homosexual (n = 10; 30.3%) or heterosexual (n = 5; 15.2%) intercourse, through intravenous drug use (n = 6; 18.2%), or blood transfusion (n = 2; 6.1%). In 8 cases (24.2%) the route of HIV transmission was unknown; two patients had two competitive possible ways of transmission. Before diagnosis of PML, 22 patients (66.7%) did not receive any antiretroviral therapy, four patients (12.1%) took one antiretroviral drug and two (6.1%) took a combination of two antiretroviral drugs. Only five patients (15.2%) were on HAART at the time of PML diagnosis. Thus, 28 patients in our study were HAART naïve.

After diagnosis of PML, 17 patients (51.5%) were treated with HAART and 14 (42.4%) with cidofovir in any combination. Of these patients, 13 (39.4%) were treated with HAART and cidofovir in combination, four patients (12.1%) received only HAART without cidofovir, and one patient received only cidofovir without HAART but with a combination of two antiretroviral drugs. Fifteen patients (45.5%) in our study received neither HAART nor cidofovir after the diagnosis of PML; they were just treated without an antiretroviral therapy (n = 6) or with a mono- (n = 4) or twofold (n = 5) therapy of antiretroviral drugs (Fig. 1). This high number of patients not treated with HAART is due to the time of introduction of HAART in 1996 (we retrospectively included patients since 1988).

After a mean follow-up of 17.0 months (range 0–82 months), 10 patients were alive and 23 (69.7%) had died. All deaths were related to PML and occurred after a mean of 9.0 months (range 0 to 38) after the diagnosis of PML. The 10 patients who were still alive at the end of follow-up had a mean survival time of 35.3 months (range 2 to 82) after diagnosis of PML.

The cumulative survival was significantly longer in the group of patients treated with HAART than in the group treated without HAART, independent of whether cidofovir was given or not (44.1 months vs. 10.5 months; p = 0.006; Fig. 2). The combination of HAART and cidofovir resulted in a longer cumulative survival than HAART alone (49.8 months vs. 24.3 months), but in comparison with single therapy with HAART, the com-