Antiretroviral Therapy in HTLV-1 Infection

Subjects: Infectious Diseases

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The human T cell leukemic/lymphotropic virus type 1 (HTLV-1), discovered several years ago, is the causative agent for a rapid progressive haematological malignancy, adult T cell leukemia (ATL), for debilitating neurological diseases and for a number of inflammatory based diseases. Although the heterogeneous features of the diseases caused by HTLV-1, a common topic concerning related therapeutic treatments relies on the use of antiretrovirals.

Keywords: HTLV-1 ; antiretrovirals ; HAM/TSP ; ATL

1. Introduction

The human T cell leukemic/lymphotropic virus type 1 (HTLV-1) [1] was the first human retrovirus to be identified, almost 40 years ago [2]. It has been estimated, some years ago, that at least 5–10 million people were infected with HTLV-1 worldwide [3]. Data on the prevalence of HTLV-1 infection mainly derive from studies carried out in ancient endemic areas such as Japan, Carribean islands, some regions in South America, sub-Saharian Africa, and the Middle East. More recently, Australia, where about 50% of Australian indigenous were recently reported to be HTLV-1 infected [4], has also been added to the list of these ancient endemic areas. However, mainly due to increased immigration and tourist fluxes in the recent years, we can reasonably suppose that the virus is not yet confined in ancient endemic areas and the current prevalence of HTLV-1 infection in the world population is actually unknown.

HTLV-1 is the etiological agent of a rapid progressive malignancy, Adult T cell leukemia (ATL), which develops in 5% of infected people, as well as a debilitating neurological disease, HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), which develops in 4% of HTLV-1 positive individuals. In addition, a number of inflammatory HTLV-1 associated diseases such as uveitis, Hashimoto's thyroiditis and Graves' disease, HTLV-1 associated pulmonary disease, infective dermatitis associated with HTLV-1, HTLV-1 associated inflammatory myositis, and HTLV-1 associated arthritis have been reported [5]. HTLV-1 is usually transmitted through sexual partners, breastfeeding, blood transfusion, and recently, it was reported also through organ transplantation. Although HTLV-1 was the first human retrovirus discovered before the most recent HIV-1, both diagnosis and therapeutic approach of infection await further clarification and investigations. There are a number of peculiar aspects of HTLV-1 infection which clearly distinguish it from HIV-1 infection and allow the virus to escape host control by causing a latent infection. HTLV-1 is a highly cell associated virus which mainly integrates influencing through its regulatory protein the function of host cells. Differently from HIV-1, HTLV-1 virus spread relies mainly on vertical transmission (mitotic spread), while a role can be also played by horizontal transmission (infectious spread). In contrast with HIV-1 which kills target CD4+ cells, HTLV-1 infection is characterized by expansions and persistence of infected T cell clones that prompt the emergence of both neurological and haematological diseases. Mechanisms regulating the clonality of HTLV-1 infected cells have not been fully elucidated [6].

2. Pioneering Studies

Zidovudine (3'-azido-3'-deoxythymidine; AZT), a nucleoside analogue acting as competitive inhibitor of reverse transcriptase was the first effective antiretroviral used in HIV infection [7]. The potential effect of AZT against HTLV-1 was firstly shown by an in vitro study using a CD4+ cell clone, established from primary lymphocytes following co-culture with a lethally irradiated HTLV-1 producing tumour cell line. This research highlighted a profound suppression of GAG production and proviral DNA in the presence of AZT [8]. Soon after, the effects of AZT towards HTLV-1 infection in vivo were demonstrated by Isono et al. in an animal model of ATL in rabbits. They hypothesized a duplex role of AZT that in rabbit could interfere with leukaemogenesis by both inhibiting reverse transcriptase, and by decreasing the growth of inoculated transformed leukemic cells [9]. Thus, the era of antiretrovirals in HTLV-1 infection was opened.

3. Translational Approaches with Nucleoside/Nucleotide Reverse Transcriptase Inhibitors in HTLV-1 Infection: Preclinical and Clinical Studies

3.1. Neurological Diseases

An HTLV-1 associated neuromyelopathy, originally named tropical spastic paraparesis (TSP), was first uncovered in the Caribbean area. A similar neurological disorder was then described in Japan and named as HTLV-1 associated myelopathy (HAM). The two diseases were then recognized to be identical and here the researchers refer to this neurological disease, occurring in HTLV-1 infected patients, as HAM/TSP. First clinical trials using AZT in HTLV-1-infected HAM/TSP patients provided conflicting reports. An open study conducted for six months on five patients (1 g/day) affected by HAM/TSP observed no effect of AZT on the encephalomyelopathy and therefore no clinical benefit [10]. Conversely, an open label study with ten HAM/TSP patients, scored for expanded disability status scale (EDSS) treated with high dose of AZT (2 g/d for four weeks, followed by 1 g/d for 20 weeks) reported an objective improvement in seven patients and no general worsening [11].

Obviously, since HAM/TSP is caused by HTLV-1 infection, the assessment of the effect of antiretroviral therapy on viral load could highlight the possible influence of inhibition of reverse transcription on the clinical response. However, in vivo response to AZT was variable, and therefore, studies with other nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) were performed. In particular, it was reported in observational studies that treatment with lamivudine (2,3-dideoxy-3-thiacytidine; 3TC) for 24 weeks was able to reduce HTLV-1 viral load in five out of five patients with HAM/TSP, but with oscillation rising toward the baseline, accompanied by parallel variation in CTL precursor frequency and CD25 expression. These data pointed out an effect of therapy towards reverse transcription and the return to base line proviral DNA was interpreted as a failure in drug phosphorylation within the cell or emergence of viral variants with less susceptibility to 3TC inhibition [12]. Moreover, it was excluded that the return to base line proviral DNA level could be owed to mutations since after extensive analysis of the consensus sequence of RT before and after 3TC treatment no substantial substitutions were found. This was an important proof of concepts, although variation in the response of HAM/TSP patients was not easily understood. Resistance of HTLV-1 to 3TC was further highlighted by in vitro assays. Five different HTLV-1 isolates were found to be susceptible to a number of NRTIs, AZT, didanosine (2′,3′-dideoxyinosine; ddI), stavudine (2,3-didehydro-3 –deoxythymidine; d4T), and zalcitabine (2,3-dideoxycytidine; ddC), but not to 3TC. Resistance of HTLV-1 RT to 3TC was acknowledged in HIV and ascribed to the conserved LPQG (Q151M) or YMDD (M184) mutations in HIV-RT, but the portion of alignment of HIV RT and HTLV-1 RT corresponding to 3TC resistance did not match excluding that resistance to 3TC treatment of HTLV-1 was owed to this type of mutation [13]. On the basis of the transient decline of HTLV-1 viremia in response to therapy with 3TC in HTLV-1 infected patients, it was hypothesized that partial resistance of HTLV-1 to 3TC was of natural type, due to polymorphism at codon 118 (valin replaced by isoleucin). This was further supported by evidence that isoleucine at position 118 induced resistance to 3TC incorporation in HIV RT which shares a similar sequence with the HTLV-1 RT [14]. Therefore, the presence of isoleucine at the position 118 could be responsible of natural resistance of HTLV-1 to 3TC, although these data have not been confirmed by biochemical and site-directed mutagenesis studies. Nevertheless, these results justified a warning regarding the NRTIs therapy, including the use of 3TC, in HTLV-1 patients. In vitro assays on the effects towards HTLV-1 infection, of several NRTIs including AZT, 3TC, d4T, ddC, abacavir ((1S,4R)-4-[2-amino-6-(cyclopropylamino)purin-9-yl]cyclopent-2-en-1-yl] methanol, ABC), and the acyclic analog of deoxyadenosine 5′-monophosphate nucleotide tenofovir (9-(R)-[2- (phosphonomethoxy)propyl] adenine, PMPA; TFV) were improved by studies using recombinant HTLV-I vectors to reproduce early steps of the viral replication. These studies analyzed the effects of antiretrovirals on HTLV-1 infection in vitro using the sophisticated tool of single-cycle infection and reached conclusions similar to those achieved through classical methods of multiple-cycle infection through HTLV-1 transmission in vitro by co-cultivation [15].

One alternative strategy for the use of NRTIs in HAM/TSP could be a combination treatment including compounds acting on different targets from viral replication. Such a possible alternative approach was the investigation of the effects of a combination treatment of NRTIs with the epigenetic regulator valproic acid (VPA). Asymptomatic baboon naturally infected with STLV-1, almost identical to HTLV-1 in humans, were treated with a combination of AZT plus VPA resulting in a reduction of proviral load by 5–12-fold in 50% of the animal tested at early stage of infection. The treatment with VPA was shown to be associated to a transient rise in the proviral load early in the first week of treatment while combination with AZT prevented the rebound of the viral load. Given that the decrease of viral load in VPA/AZT treatment was accompanied by an increase of CD8+ effector-cell cytotoxic activity, it was hypothesized that the decrease in viral load was owed to the reactivation of the immune response against the virus facilitated by AZT-mediated inhibition of viral transmission. On the other hand, the rebound of viral load following interruption of the combined treatment might be due to virus production by reservoirs not affected by the therapy, similar to what is observed in HIV infection. On the basis of

the results obtained in STLV-1 infection, the combination treatment with VPA and AZT could be potentially transferred to HAM/TSP patients if treated at an early stage of the disease [16].

3.2. Haematological Diseases

In contrast to HAM/TSP, NRTIs were fruitfully used to treat ATL caused by HTLV-1 infection. This choice was due to the poor therapeutic options for treating ATL which was resistant to the classical cytotoxic chemotherapy. One of the first reports about the use of antiretrovirals was done by Gill et al. in 1995 when AZT was combined with interferon alpha (IFNa) [17]. This combination caused 28% of complete remission and in general a major response in 58% of the 19 treated individuals, with overall median survival of three months. However, these results were rather similar to those obtained following treatment with chemotherapy. Therefore, no conclusion on the superiority of AZT plus IFNa over classical chemotherapy could be drawn. Similar results were obtained in AZT plus IFNa treatment of five ATL patients, one with smoldering and four with acute ATL, of whom three resulted complete responders while two partial responders [18]. The longest survival was 27 months after the diagnosis. One key, unanswered question was whether the combination AZT+IFNa was efficacious owed to its antiviral effect or whether acted as cytotoxic drugs. To clarify this aspect, assumptions and further studies have been made. Among the first issues investigated were the effects of AZT plus IFNa on cell proliferation, on the expression of apoptosis regulators proteins, on cell growth, and on the cell cycle [19]. Results of this research, performed using HTLV-1 chronically infected cell lines as well as PBMC from ATL patients, apparently excluded a direct cytotoxic effect of AZT plus IFNa in ATL. Although mechanisms of the combination therapy with AZT+IFNa in ATL were not disclosed, successive studies further confirmed the efficacy of this treatment. A longer follow up of 15 adult T cell leukemia/lymphoma, ATL patients treated over four years with the combination of AZT plus IFNa, resulted in 18 months median survival time with no major side effects [20]. Again, events involved in the improvement of patients treated with the combination treatment were not clarified; however, it was hypothesized that an increase of the CTL response against the virus could be involved. Moreover, considering the response exerted by the combination treatment versus that of the classical chemotherapy, and that a preventive chemotherapeutic treatment able to reduce the tumour burden, proved to enforce the response to AZT+IFNa, furthers studies on the effects of a combination chemotherapy followed by AZT+IFNa in ATL were planned. The effect of AZT+IFNa combination treatment in ATL patients was later confirmed in a study carried out in a different country that demonstrated inhibition of viral load and decrease of angiogenesis. Interestingly, the efficacy of AZT+IFNa was overall proved by a meta-analysis performed on 254 patients with ATL. Actually, in acute ATL, achievement of complete remission by antiviral therapy caused 82% five-year survival, while in chronic and smoldering ATL, antiviral therapy resulted in 100% five-year survival [21]. Moreover, a retrospective study on the outcome of AZT+IFNa treatment in 73 patients with aggressive ATL recruited in England from 1999–2009, was reported.

3.3. Haematological Diseases: Direct or Indirect Effect of AZT+IFNa?

The above reported studies highlighted the need to elucidate whether AZT+IFNa combination exerted a direct antiretroviral effect. Actually, an indirect antiretroviral effect by AZT+IFNa combination was recently hypothesized as the consequence of an impact towards dendritic cells or macrophages in which viral replication occurs and that provide growth factors and cytokines useful for the survival of ATL cells [22]. Interestingly, recent data have supported a role for IFNa in suppressing in vitro intracellular HTLV-1 Tax protein expression in IL-2 dependent HTLV-1 infected T cells, mediated by upregulation of an RNA-dependent protein kinase (PKR) [23]. In addition, IFNa alone upregulated the NF-kB system in IL-2 dependent HTLV-1 infected T cells in vitro.

3.4. Transplantation

Transplantation has been recently recognized as a potentially efficacious HTLV-1 transmission route. The lack of routinely screening of organ donors for HTLV-1 makes difficult to precisely state that the transplant is actually responsible for ATL or HAM/TSP development in the recipient. Some scattered case reports were reported in the literature regarding HTLV-1 transmission through organ transplantation in France, Spain, and United States [24][25][26][27]. Antiretroviral therapy based on AZT and the integrase inhibitor raltegravir (for this compound, see also the next paragraph) was recommended as postexposure prophylaxis within 48 h from transplant before establishing of infection through generation of proviral DNA [28]. Actually, the screening of organ donors was introduced in 2012 in UK after a case of transmission of HTLV-1 from a single solid organ donor to three transplant recipients. A liver and two kidneys were taken from a deceased woman, and their HTLV-1 positivity was established early after transplant. The recipients underwent an early treatment with AZT and raltegravir for 24–54 days and at 30 months after the treatment no outcome of HTLV-1 associated diseases was observed. However, molecular and serological studies revealed the presence of HTLV-1, 16 days after transplantation [29]. Antiretroviral treatment was initiated at day 23, i.e., when infection was already established and, therefore, presumably

without impact on already infected cells. In fact, antiretroviral treatment did not arrest rapid dissemination of HTLV-1, with a proviral load plateau at six weeks and unique integration site analysis indicating early clonal expansion and high rate of infectious spread. This lays for the need of using antiretroviral as prophylactic treatment in case of pre transplantation assessment of HTLV-1 positivity of the donor or at very early time after transplantation in case of post-transplantation assessment. Recently, the development of HAM/TSP was described in a case of kidney transplant from a cadaveric donor which was found HTLV-1 positive 24 h after transplantation. The recipient underwent antiretroviral prophylaxis with AZT, 3TC, and raltegravir that was maintained only for one month. The patient did not seroconvert for a month and virus was not present until day 83 from transplant. However, three months after transplantation the patient was found positive for HTLV-1 provirus. Antiretroviral therapy was resumed and maintained for six months, but neurological symptoms progressed even in presence of steroid treatment [30]. Presumably, antiretroviral treatment delayed virus appearance but successive virus spread was not controlled due to early interruption of therapy. Another case report from Spain accounted for a woman who received renal transplant from HTLV-1 positive donor and started antiretroviral therapy with AZT, 3TC and raltegravir for 18 months. Eight months after transplantation, the patient developed HAM/TSP showing high proviral load. The second kidney transplant recipient from the same donor was treated with antiretroviral therapy for two months after transplantation. A low viral load was found, the patient underwent transplant rejection, but he did not develop any disease associated to HTLV-1 infection after three years. Altogether, these reports indicate that antiretroviral treatment started after transplantation, and even at ab early time, cannot overcome HTLV-1 infection transferred with the transplant, but rather delay infection depending also on the length of treatment. Since the reported cases of transplant recipient from HTLV-1 positive donors subjected to antiretroviral therapy including NRTIs are few, and there remains a lack of established protocol for antiretroviral treatment, it is still difficult to draw definitive conclusions concerning this subject.

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