Regression of AIDS-related Kaposi’s Sarcoma Following Antiretroviral Therapy with Protease Inhibitors: Biological Correlates of Clinical Outcome

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The clinical response of AIDS-related Kaposi’s sarcoma (KS) to highly active antiretroviral therapy (HAART), a combination of human immunodeficiency virus type 1 (HIV-1) protease and reverse transcriptase inhibitors, was studied in 11 patients, all but one with progressive KS. CD4+ cell counts, plasma HIV-1 RNA levels, and antibody titres to lytic ORF65 and latency-associated human herpes virus type 8 (HHV-8) proteins were determined in sequential samples. Six complete and three partial clinical responses were achieved in a median time of 6 and 3 months, respectively, and confirmed after a median time of 16 months on HAART. 2 patients showed disease progression. A consistent decrease in HIV-1 RNA levels, paralleled by an increase in CD4+ cell counts, was observed in all patients who showed complete or partial clinical response; HIV-1 RNA levels remained persistently high in the two patients who progressed, despite a change in HAART. HHV-8 antibody titres were generally higher in patients with mucosal/visceral involvement compared with patients with limited disease; a decrease in ORF65 antibody titre was significantly associated with a clinical response. These results indicate that HAART is effective for AIDS-related KS; the clinical response correlates with a decrease in plasma HIV-1 RNA levels, an increase in CD4+ lymphocytes, and a decrease in antibodies to ORF65 HHV-8 protein. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: Kaposi’s sarcoma, HIV-1, HHV-8 antibodies, protease inhibitors, HAART


INTRODUCTION

People living with human immunodeficiency virus type 1 (HIV-1) infection are at high risk of developing Kaposi’s sarcoma (KS), the most common malignancy associated with the acquired immune deficiency syndrome (AIDS) [1]. Unlike the sporadic and endemic KS variants that show an indolent course and mainly affect the soft tissues of the lower limbs, AIDS-related KS is similar to that seen in pharmacologically immunosuppressed organ transplant recipients [2]; indeed, it too progresses rapidly, and shows a wide spectrum of lesions, ranging from asymptomatic cutaneous patches to multiple skin plaques and nodules, as well as mucosal and visceral involvement [2].

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The aetiology and pathogenesis of AIDS-related KS are still ill-defined. It was advanced that, besides determining immunodeficiency, HIV-1 might be involved through its transactivator Tat protein, which is released by infected cells and taken up by nearby cells [3], and whose angiogenic properties are well established [4]. Moreover, HIV-1 infection might produce an increase in inflammatory cytokines, such as interleukin (IL)-1, IL-6, oncostatin M and interferon (IFN)-γ, which in turn would promote the growth of hyperplastic/neoplastic KS cells [5]. A novel herpes virus, called KS-associated herpes virus (KSHV) or human herpes virus type 8 (HHV-8), has recently been linked to KS [6,7]. Indeed, HHV-8 was detected in the spindle cells, endothelial cells, and monocytes of almost all KS lesions, and in the peripheral blood mononuclear cells of approximately 50% of KS patients [8]; moreover, whilst several studies found...
antibodies against HHV-8 in almost 100% of KS subjects, its seroprevalence in the general population of the U.S.A. and Europe varies from 1 to 25%, depending on the geographical area, and the methodology employed [9]. The finding that the HIV-1-encoded Tat protein exerts a positive effect on HHV-8 replication suggests an interplay between the two viruses [10].

Several studies have been conducted to define a chemotherapeutic approach to AIDS-related KS. Treatments with cytotoxic drugs, alone or in combination, were found to have variable response rates, and increased the frequency of opportunistic infections [11,12]. The addition of antiretroviral zidovudine treatment to combination chemotherapy did not improve the response rates [13]. The course of HIV-1 infection has been greatly modified by highly active antiretroviral therapy (HAART), a recently introduced triple-drug combination treatment using two reverse transcriptase inhibitors (RTI) and a protease inhibitor (PI). HAART brings about a significant and sustained decrease in peripheral blood HIV-1 RNA levels, as well as an increase in CD4+ T cells, and significantly delays the development of AIDS-associated opportunistic infections and death [14]. Preliminary reports suggested that PIs might also lead to a reduction in KS lesions [15–19]; moreover, complete remission of KS lesions was recently reported in patients on HAART [20].

The aim of this study was to evaluate the clinical impact of HAART on AIDS-related KS lesions, as well as the relationship between clinical response, HIV-1 viral load and antibody titre against lytic and latent HHV-8 proteins.

**PATIENTS AND METHODS**

**Patients**

Between October 1996 and July 1997, all HIV-1 seropositive patients with stable or progressive biopsy-proven KS and measurable disease attending the Department of Infectious Diseases of Padova Hospital were consecutively enrolled in a open prospective study. At study entry, a complete medical history was obtained, and the patients underwent a physical examination, including measurement of all cutaneous and mucosal lesions. In addition, all patients with a clinical suspicion of visceral KS underwent gastrointestinal/bronchial endoscopy, and chest tomography. The patients were clinically staged according to the AIDS Clinical Trial Group (ACTG) criteria based on tumour extent (T), severity of immunosuppression (I), and other systemic HIV-1 associated diseases (S) [21,22]. None of the patients had previously received PIs.

11 male patients (median age 43 years; range 28–57 years) were enrolled in this study; 7 were homosexual, 3 were bisexual, and 1 reported a history of intravenous drug use and homosexual behaviour. Characteristics of the patients at baseline are reported in Table 1. The median interval between KS diagnosis and study entry was 9 months (range: 1–47 months). Before entering the study, 9 patients had been treated with nucleoside RTI, and 4 had received systemic KS chemotherapy, consisting of 10 mg/m² bleomycin (B) and 6 mg/m² vinblastine (V) on days 1 and 15 every 2 weeks for a total of six cycles, according to a previous protocol [23] (Table 1). Patient 8 concluded BV chemotherapy 3 months prior to study entry. After six BV cycles, patients 4 and 7 were treated with bleomycin therapy (intravenous infusion of 10 mg/m² every 2 weeks), and liposomal daunorubicin (40 mg/m² every 2 weeks), respectively. All patients had a history of previous opportunistic infections, except patients 4 and 8 in whom KS was the AIDS-defining illness. 10 patients were in the poor risk group, as defined by any evidence of the following: visceral disease, tumour-associated oedema, and CD4+ cell count <150 cells/µl [22]. Of the 2 patients with visceral disease, 1 (pt 4) had large lesions located in the main left bronchial wall visualised by bronchoscopy, and another (pt 9) had multiple pulmonary interstitial infiltrates confirmed by chest tomography. A single patient (pt 1, Table 1) fell into the ToIoSo group, according to ACTG criteria [21,22]; this patient had stable KS following a partial remission that appeared during treatment with a dual nucleoside RTI, 3 months prior to study entry.

**Treatments**

The HAART regimen consisted of a triple-drug combination, including two nucleoside RTIs and one PI, according to current guidelines [24,25]. The antiretroviral drugs used in

<table>
<thead>
<tr>
<th>Pt code</th>
<th>Age</th>
<th>Previous antiretroviral therapy</th>
<th>KS staging</th>
<th>Previous KS chemotherapy</th>
<th>Visceral</th>
<th>Lympho</th>
<th>Oedema</th>
<th>Mucosal</th>
<th>PATCH</th>
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ZDV, zidovudine; DDC, dactinabine; DDI, didanosine; 3TC, lamivudine; B, bleomycin; V, vinblastine; D, liposomal daunorubicin. *Time from the date of Kaposi's sarcoma (KS) diagnosis.
the different combinations were administered daily at the following doses: RTIs—zidovudine 600 mg, lamivudine 300 mg, zalcitabine 2.15 mg, didanosine 400 mg, stavudine 80 mg; PIs—indinavir 2400 mg, ritonavir 1200 mg, saquinavir 2400 mg, nelfinavir 2250 mg. 3 patients with symptomatic visceral/mucosal involvement continued their previous KS chemotherapy; concomitant prophylaxis for opportunistic infections was allowed.

Assessment of response
During the study period, a complete physical examination was made every month; tumour measurements, blood counts, and CD4+ lymphocyte counts were also recorded. If endoscopic and radiographic findings at study entry were abnormal, these examinations were repeated. Clinical responses were evaluated using the ACTG criteria [21]. A complete clinical response was defined as the absence of any detectable residual disease, including tumour-associated oedema, without the presence of new lesions, persisting for at least 4 weeks; for visceral KS, normal endoscopic and radiographic findings were considered a complete response. A partial response was defined as the absence of new lesions and ≥50% decrease in the number of all pre-existing lesions, or complete flattening of ≥50% of the lesions, or ≥50% decrease in lesion size, determined by calculating the products of two perpendicular dimensions, for at least 4 weeks. Progressive disease was defined as an increase of ≥25% in the size of pre-existing lesions, or the development of new ones. Any response not meeting the criteria for complete response, partial response, or progressive disease was considered stable disease.

Quantitative HIV-1 RNA assay
EDTA peripheral blood samples were centrifuged over a Ficoll-Hypaque (Pharmacia, Uppsala, Sweden) density gradient; plasma was recovered from the upper phase and centrifuged at 1000 g to ensure a cell-free specimen. Two hundred microlitres were employed for HIV-1 RNA determination, and the remainder was aliquoted and stored at −80°C. HIV-1 RNA was determined using a quantitative reverse transcriptase polymerase chain reaction assay (Amplicor Monitor, Roche Diagnostic System, Branchburg, New Jersey, U.S.A.), whose lower limit of detection was 200 HIV-1 RNA copies/ml.

Analysis of HHV-8 antibodies
Plasma samples were analysed for antibodies to a latency-associated nuclear antigen (LANA), and a capsid-related protein encoded by ORF65, as previously described [26, 27]. LANA antibodies were evaluated by an indirect immunofluorescence assay (IFA) on paraformaldehyde-fixed BCP-1 cells; plasma samples were initially analysed at a dilution of 1:100, and subsequently at serial 2-fold dilutions. ORF65 antibodies were tested by enzyme-linked immunosorbent assay (ELISA) at an initial plasma dilution of 1:100, and then at serial 2-fold dilutions; the cut-off value was the average optical density value of plasma samples from 10 HHV-8 seronegative Italian blood donors plus 5 standard deviations. Purified recombinant dehydrofolate reductase (DHFR), the fusion partner of recombinant ORF65 protein, was employed as control antigen; reactivity of plasma samples to this DHRF region was considered non-specific and, accordingly, plasma

Table 2. Clinical response

<table>
<thead>
<tr>
<th>Pt code</th>
<th>HAART regimen (months)</th>
<th>KS chemotherapy* (months)</th>
<th>KS response PR</th>
<th>CR</th>
<th>PD</th>
<th>At last examination (Months)</th>
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<td></td>
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<td>CR (16)</td>
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PR, partial response; CR, complete response; PD, progressive disease; B, bleomycin; D, liposomal daunorubicin; V, vinblastine; P, paclitaxel; IDV, indinavir; SQV, saquinavir; RTV, ritonavir; NFV, nelfinavir; ZDV, zidovudine; DDC, zalcitabine; DDI, didanosine; 3TC, lamivudine; D4T, stavudine; HAART, highly active retroviral therapy; KS, Kaposi’s sarcoma. *Chemotherapy during HAART. †Patient 6 underwent surgery 2 months after starting HAART. No new lesions occurred during the follow-up period.
samples reactive against recombinant ORF65 protein and DHRF were considered negative by ELISA. To verify whether antibody titres were linked to the clinical response, statistical analyses were performed using the F test of Snedecor and Cochran [28].

**RESULTS**

**Clinical response**

Treatments and clinical response during the study are shown in Table 2. The HAART regimen was changed after 1 month in 1 patient (pt 3, Table 2) because of intolerance, and in 4 others (pts 1, 4, 7, 8, Table 2) due to the lack of a satisfactory HIV-1 response. During the study period, 2 patients (pts 4 and 9) concluded their previous KS chemotherapy, and 1 (pt 7) was maintained on chemotherapy (Table 2). The median follow-up period was 16 months (range 10–21 months). During the study, 6 patients showed a complete response in a median time of 6 months (range 3–14 months). Pt 1 showed a complete response as early as 3 months after starting HAART; in 4 others (pts 3–5 and 11, Table 2) complete remission followed a partial response achieved at months 2, 5, 8 and 1, respectively. Resolution of the pulmonary lesions in pt 4 was confirmed by endoscopic/histological examinations. Patient 6, who presented a single KS lesion on the right leg, underwent ablative surgery 2 months after starting HAART; no new lesions occurred during the follow-up period. All patients who achieved complete remission were still in this condition at the end of follow-up (Table 2). 3 patients (pts 2, 9, and 10, Table 2) achieved partial responses at 3, 6, and 1 months, respectively, after starting HAART, and were still in this clinical condition when last seen. Pt 7 showed disease progression for 9 months; chemotherapy with paclitaxel (30 mg/m² every week) was then started, and a partial response was achieved after 2 months. Pt 8 showed a partial remission at 6 months, but progressive disease at 15 months. Haematological and non-haematological toxicity greater than grade 1, according to the WHO common toxicity criteria, was not observed. Moreover, no opportunistic infections occurred during the study.

**CD4 lymphocytes and HIV-1 burden**

At study baseline, the median CD4+ cell count was 32 cells/μl (range: 2–214 cells/μl), and the median plasma HIV-1 RNA level was 108 000 copies/ml (range: 23 000–315 000 copies/ml). Undetectable HIV-1 RNA values were achieved in 5 of 6 subjects who took the same drug combination for the entire follow-up period (pts 5, 6, and 11, Figure 1; pts 2, and 9, Figure 2), and in 3 others after changing the drug combination (pts 3, 4, and 1, Figure 1). The decrease in HIV-1 RNA levels was paralleled by an increase in CD4+ cell counts. After 7 months on HAART, pt 5 suspended the therapy for 3 months; during this interval, HIV-1 RNA values increased and the CD4+ cell count decreased (Figure 1b).

At the time of the partial response, the median CD4+ cell count was 104 cells/μl (range: 27–292 cells/μl) and the median HIV-1 RNA level was 5300 copies/ml (range: 200–
376,000 copies/ml); no significant difference in either parameter was observed between patients who subsequently achieved complete remission and patients who remained with partial response. When complete responses were obtained, the median CD4+ cell count was 215 cells/μl (range 127–423 cells/μl), and HIV-1 RNA levels were undetectable in all but one subject (pt 1, Figure 1a); this patient, however, had relatively low HIV-1 RNA values that decreased to an undetectable level after changing the triple-drug combination. Viral burden remained at very low or undetectable levels in all patients, except one (pt 3, Figure 1c) who showed an upsurge after 9 months on HAART. Undetectable levels of HIV-1 RNA were also maintained during the follow-up period in 2 (pts 2, and 9, Figure 2) of 3 patients with partial response; in one (pt 10, Figure 2d), a 1-log decrease in viral load was achieved within 4 weeks of therapy and followed by an increase that exceeded the baseline level at the end of follow-up. In pt 8 (Figure 2c) who showed disease progression after a partial response, and in pt 7 (Figure 2c) with progressive KS plasma HIV-1 RNA levels remained consistently high, and the CD4+ cell count remained below 50 cells/μl, despite a change in the HAART regimen.

Pattern of HHV-8 seroreactivity

HHV-8 antibody titres to ORF65 protein, associated with lytic infection, and LANA were determined before HAART initiation, and at different time intervals during follow-up. All patients beginning HAART with limited cutaneous involvement or minimal mucosal disease (pts 1, 6, and 11, Figure 1; pt 10, Figure 2d) had detectable LANA antibody levels, whilst all, except pt 1, had undetectable or very low titres of antibodies to ORF65. These data might indicate that low tumour burden is accompanied by low titres of antibodies to a lytic-phase antigen. Patient 1, who achieved complete remission 3 months after starting HAART, showed increasing levels of LANA and ORF65 antibodies, which might possibly be indicative of viral reactivation.

Patients entering HAART with disseminated cutaneous KS and mucosal and/or visceral involvement showed widely varied HHV-8 antibody levels at baseline and during follow-up. A decrease in ORF65 antibody titres was observed around the time of complete remission (pts 3–5, Figure 1); patient 4, however, showed increased levels of ORF65 and LANA antibodies 5 months later, even though complete response was still confirmed. Patient 2 also showed a transient decrease in ORF65 antibodies, after the first evidence of clinical partial response (Figure 2a). Conversely, increasing levels of ORF65 antibodies were observed in pt 9 (Figure 2b), who had only a partial response, and in the 2 patients who showed disease progression. In particular, pt 7 (Figure 2c) showed a gradual and remarkable increase in the ORF65 antibody titre during disease progression, which may be indicative of highly active HHV-8 infection/reactivation; following paclitaxel administration and the achievement of partial remission, ORF65 antibodies declined. Pt 8 (Figure 2c) showed an initial small increase in both ORF65 and LANA antibody titres; thereafter, the antibody level to both antigens remained relatively stable over time.

Figure 2. CD4+ cell count, HIV-1 RNA plasma level, and anti-HHV-8 antibody titre in Kaposi's sarcoma (KS) patients who achieved partial clinical response during HAART. Arrows indicate KS clinical response: partial response (○); progressive disease (▲). ▶ indicates antibody not detectable at 1:100 plasma dilution.
Statistical analyses revealed that the decrease in ORF65 antibody titres was significantly correlated to the clinical response \(F(3,57) = 5.38\), whereas the treatment did not influence the LANA antibody titre \(F(3,57) = 0.61\).

**DISCUSSION**

Systemic chemotherapy for AIDS-related KS is usually followed by a low rate of short-lived clinical responses [11,12]. Treatments with biological response modifiers or differentiation agents, such as IFN-α or retinoic acid derivatives, alone or in combination with standard chemotherapy have not produced any significant increase in the response rate [29]. Recent attempts to introduce anti-angiogenic compounds, or human chorionic gonadotropin preparations in the treatment schedule represent interesting approaches, but require further evaluation [30–32].

The advent of multidrug antiretroviral regimens, based on a combination of reverse transcriptase and protease inhibitors, has greatly improved the clinical outcome of HIV-1 infection, as indicated by a substantial decline in AIDS incidence and mortality [14]. These potent antiretroviral agents induce a clearance of HIV-1 from the plasma and other biological fluids, even if complete eradication is precluded by the persistence of latently infected cells. In individuals who experience an optimal virological response to HAART, the immune response directed against a variety of infectious pathogens is also restored, as shown by in vitro assays [33], and the remarkable decrease in opportunistic infections [14].

HAART also appears to influence the clinical course of AIDS-related KS; indeed, recent reports describe KS patients with partial or complete regression [15–20], and the results of the present study are in line with these observations. In a group of 11 KS patients treated with HAART, 6 complete and 3 partial responses were achieved and confirmed at the end of the study period. A substantial decrease in the plasma HIV-1 RNA load coincident with a rise in the CD4+ cell count was observed in all 6 patients with complete remission, whilst consistently high levels of plasma viraemia and low CD4+ cell counts were found in the 2 patients with disease progression. Thus, a good correlation between efficacy of HAART and KS clinical response was evident. It is noteworthy that 5 of 6 patients with complete remission were never given antitumour chemotherapy. The introduction of paclitaxel in the treatment schedule of patient 7 caused a shift from KS progression to partial remission, even if the contemporaneous change in the HAART combination was not followed by a decrease in the plasma HIV-1 load. Our data indicate that the evolution of AIDS-related KS is greatly dependent on the HIV-1 burden, and the ensuing degree of immunodeficiency. In addition, previous studies on the angiogenic properties of HIV-1 Tat regulatory protein [4] and the activation of the inflammatory cytokine cascade are consistent with the present findings, and further emphasise the relevant, albeit indirect role of HIV-1 infection in KS pathogenesis [5]. However, the possibility that some antiretroviral protease inhibitors are also endowed with an intrinsic anti-KS activity cannot be ruled out.

Following the identification of HHV-8, an increasing body of evidence pointing to an aetiological link between this virus and KS development has accumulated. Like other gamma-herpes viruses, namely herpes virus Saimiri and Epstein–Barr virus, HHV-8 also seems to possess an oncogenic potential; indeed, analysis of its genomic sequences reveals a set of genes that are structurally and functionally related to cellular genes known to interfere with cell cycle control, or endowed with growth promoting and anti-apoptotic activity [34]. Furthermore, two different viral genes, i.e. K1 and K12, when expressed in rodent fibroblasts, produced morphological changes and focus formation indicative of neoplastic transformation, and were tumorigenic in vivo [35,36].

Using available first-generation serological assays, we measured plasma antibody titres to lytic (ORF65) and latency-associated nuclear (LANA) antigens in an attempt to discern an antibody trend that might be indicative of the HHV-8 replicative status during KS evolution. Whilst the LANA antibody titre showed a variable pattern, ORF65 antibody levels were found to be significantly correlated with clinical response. Indeed, patients with limited KS lesions, as well as disseminated KS and mucosal/visceral involvement showed a statistically significant decline in ORF65 antibody titres during KS remission. Hence, a variation in ORF65 antibody levels, elicited by active virus replication, might be predictive of disease evolution. It remains to be determined, however, whether HHV-8 expression and replication is directly influenced by antiretroviral protease inhibitors.

In conclusion, our data confirm that the HAART regimen can induce a clinical response in AIDS-related KS, and provide evidence that the remission thus obtained is more prolonged than that achieved by conventional antitumour chemotherapy alone.

15. Murphy M, Armstrong D, Sepkowitz KA, Ahkami RN, Myskowski PL. Regression of AIDS-related Kaposi's sarcoma


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