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Prevention and Treatment of KSHV-associated Diseases with Antiviral Drugs*

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Abstract: Kaposi's sarcoma-associated herpesvirus (KSHV) was first identified as the etiologic agent of Kaposi's sarcoma (KS) in 1994. KSHV infection is necessary, but not sufficient for the development of Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD). Advances in the prevention and treatment of KSHV-associated Diseases have been achieved, even though current treatment options are ineffective, or toxic to many affected persons. The identification of new targets for potential future therapies and the randomized trial to evaluate the efficacy of new antivirals are required.

Key words: Antiviral drugs; Kaposi's sarcoma-associated herpesvirus (KSHV); Kaposi's sarcoma (KS); Primary effusion lymphoma; Multicentric castleman disease

Kaposi's sarcoma-associated herpesvirus (KSHV, also known as Human herpesvirus 8) was first identified as the etiologic agent of Kaposi's sarcoma (KS) in 1994 by Chang *et al* (14). KSHV is able to infect several cell types and is usually present as nuclear episomal structures in a latent form, while the lytic replication can take place in the peripheral blood and in tissues from KS or in Castleman's disease, but generally occurs only in 5%–10% of the infected cells (48). *In vivo* and *in vitro* studies have demonstrated that KSHV can be latently maintained at undetectable levels in circulating B lymphocytes and monocytes, which may therefore serve as a reservoir for the virus. Furthermore, circulating monocytes may recruit the virus into tissues, and upon exposure to inflammatory cytokines, undergo lytic infection and transmit the virus to other cell types (50).

Based on epidemiological studies, KSHV is now known to be prevalent in populations of gay men, as well as persons from the Southern Mediterranean, Africa, Middle East, South America and Asia (9, 17, 19, 27, 63). The use of classic epidemiology and laboratory techniques enabled scientists to associate this virus with KS, multicentric Castleman disease (MCD) and primary effusion lymphoma (PEL).

However, while KSHV infection is required for development of KS, PEL or some forms of MCD, it is not likely to be sufficient. The presence of co-factors such as immunosuppression may enhance progression to disease, and therefore there are disparities between

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the prevalence of KSHV infection and the incidence of KS. KS is the commonest KSHV-associated disease, though the incidence has dropped dramatically with the introduction of highly active antiretroviral therapy (HAART) (20). In many parts of Africa, KS is the most common cancer in the entire population. MCD and PEL remain relatively rare complications of KSHV infection. No comprehensive registry tracks the incidence of these diseases, and thus their frequency in the population is difficult to ascertain.

Since the introduction of antiviral therapy in 1978, numerous clinical studies have documented the efficacy of DNA synthesis inhibitors against human herpesvirus infections. Evidence has now accumulated supporting a role for antiviral drugs in the treatment and prevention of KSHV-associated diseases, providing optimism that novel antiviral therapies for these diseases may be found.

ANTIVIRAL DRUGS FOR KSHV AND KSHV-ASSOCIATED DISEASES

DNA synthesis inhibitors

Aciclovir, a synthetic guanine analog, was seen as the start of a new era in antiviral therapy, as it is extremely selective and low in cytotoxicity (62). Aciclovir is selectively converted into acyclo-guanosine monophosphate (acyclo-GMP) by viral thymidine kinase, which is far more effective (3000 times) in phosphorylation than cellular thymidine kinase. Subsequently, the monophosphate form is further phosphorylated into the active triphosphate form, acyclo-GTP, by cellular kinases. Acyclo-GTP is a very potent inhibitor of viral DNA polymerase; it has approximately 100 times greater affinity for viral than cellular polymerase. As a substrate, acyclo-GMP is incorporated into viral DNA, resulting in chain termination.

Now there are more than a dozen of antiherpetic drugs have been licensed for clinical use as anti-herpesvirus agents. These include guanosine analogues: lobucavir (55), H2G [(-)-2HM-HBG] (2), A-5021(31), D/L-cyclohexenyl G (70) and S2242 [2-amino-7- (1,3-dihydroxy- 2- propoxymethyl) purine] (52, 53) and non-guanosine derivatives: brivudin, foscarnet and cidofovir. It is the herpesvirus-encoded kinase that determine the sensitivity to the antiviral compounds (DNA synthesis inhibitors). Unlike other herpesviruses, KSHV does not cause a cytopathic effect in cell culture. The effect of drugs on KSHV replication can be assessed in the 12-O-tetradecanoylphorbol-13-acetate (TPA)-inducible KSHV containing BCBL-1 cells. The most potent compounds against KSHV with the highest antiviral selectivity index were S2242, cidofovir and ganciclovir (36, 47, 54). Acyclovir was found to be devoid of anti-KSHV-8 activity (EC50: > 25 mg/mL) (36).

Antiretroviral therapy

HIV contributes to the pathogenesis of KS and other KSHV-associated diseases. Since the beginning of the AIDS epidemic in the early 1980s, AIDS-KS has become one of the most common AIDS-associated malignancies with HIV-infected homosexual males at the highest risk, and those with AIDS had a 50% lifetime rate of developing KS early in the HIV epidemic (35). However, the rate of AIDS-KS has since steadily declined both in the US and Europe (7). And since the introduction of highly active antiretroviral therapy (HAART), a further major decrease in AIDS-KS was further observed (41), and therapy has now made AIDS-KS a relatively rare tumor in treated HIV-infected individuals. Now antiretroviral therapy

becomes the mainstream therapy for patients with KSHV-associated diseases. Currently there are 23 FDA-approved individual antiretroviral drugs that are classified into four categories based on their mechanism of action. There are 7 combinations of drugs currently approved by FDA. RTs and PIs showed activities in prevention and treatment of KSHV-associated diseases.

Reverse Transcriptase Inhibitors. Reverse transcriptase inhibitors (RTIs) are a class of antiretroviral drug used to treat HIV infection and HIV-KSHV co-infection. RTIs inhibit activity of HIV reverse transcriptase and some other viral polymerases. RTIs come in three forms: Nucleoside analog reverse transcriptase inhibitors (NARTIs or NRTIs), which include Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir and Emtricitabine; Nucleotide analog reverse transcriptase inhibitors (NtARTIs or NtRTIs), which include Tenofovir, Adefovir; Non-nucleoside reverse transcriptase inhibitors (NNRTIs), which include Efavirenz, Nevirapine, Delavirdine and Etravirine. NRTIs must be activated in the cell by the addition of three phosphate groups to their deoxyribose moiety, to form NRTI triphosphates. This phosphorylation step is carried out by cellular kinase enzymes. Interestingly, two experiments have shown that the thymidine analogs zidovudine (26, 43) and stavudine (43) both were phosphorylated by KSHV TK and competitively inhibited the incorporation of radiolabeled thymidine.

Protease Inhibitors. Antiretroviral protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir etc.) prevent viral replication by inhibiting the activity of HIV-1 protease. Herpesviruses use a serine protease during lytic replication to begin assembly of viral particles, which would not be affected by HIV PIs (66). Co-culturing BCBL-1 cells with indinavir had no effect on the expression of latent or lytic KHSV genes before or after stimulation with TPA, supporting that the effect of these drugs on KS was not through a direct effect on KSHV replication (65).

HIV causes immunosuppression necessary for the clinical expression of diseases. In addition, HIV tat protein induces a number of cytokines known to promote HIV replication, while also inducing KS cell growth, invasion and angiogenesis (6, 21, 29). Suppression of HIV replication or of HIV tat protein expression could thus be considered as potential therapeutic targets. It is conceivable that several mechanisms may mediate both direct and indirect effects of PIs on KSHV replication. These mechanisms include inhibiting viral replication (29), preventing the development of KS (58, 64, 65) and immune reconstitution (71).

PREVENTION OF KAPOSI'S SARCOMA WITH ANTIVIRAL DRUGS

Evidence supporting the efficacy of antiviral medication in the prevention of KSHV-associated diseases in human is found either in retrospective studies or case series. Patients treated with either DNA synthesis inhibitors or antiretroviral agents early in the HIV epidemic were seen to have significant reductions in the risk of developing KS.

Herpesvirus antiviral medications

In each of the KSHV-associated diseases, ongoing viral replication seems to play a key role in the development or sustenance of disease. The presence of replicating KSHV in the peripheral blood has been shown to be one of the strongest predictors for the

development of KS (3, 39, 72), and *in vitro* work has revealed that a small amount of lytic KSHV infection is required for the initiation and maintenance of KS tumours (25). MCD is characterized by episodic reactivation of KSHV replication, accompanied by high levels of KSHV in the peripheral blood (56) and an almost exclusively lytic viral gene program (33). PEL falls somewhere between KS and MCD in the spectrum of lytic replication (33). These observations imply that antiviral therapy aimed at abrogating KSHV replication may play a role in the prevention or treatment of KSHV-associated disease. In this regard, *in vitro* drug sensitivity studies have shown that KSHV is very sensitive to cidofovir, moderately sensitive to ganciclovir and foscarnet, and only weakly sensitive, or ineffective to acylovir (36, 47).

Several independent studies suggest that both foscarnet and ganciclovir have activity in preventing the occurrence of Kaposi's sarcoma, but that aciclovir has no benefit. Among 3,688 HIV-positive men in England, the risk of developing KS in persons using intravenous foscarnet or ganciclovir for the treatment of Cytomegalovirus (CMV) retinitis was reduced by over 60% (49). Similarly, among 935 HIV-positive American men enrolled in the multicenter AIDS cohort study, the risk of developing KS was reduced by 44% with ganciclovir use and 60% with foscarnet (23). Neither study found acyclovir use to be effective in lowering the risk of developing KS. A separate study of high-dose acyclovir for the treatment of HIV showed that acyclovir decreased herpes simplex virus infections and varicella-zoster virus infections but not cytomegalovirus disease or mortality from lymphoma or Kaposi's sarcoma (30).

A recent prospective randomised trial, aimed at determining optimal maintenance therapy for cytomegalovirus (CMV) retinitis has provided information suggesting that treatment of KSHV may prevent the development of KS (45). In this trial, a comparison of oral to intravenous ganciclovir administered for the treatment of HIV-associated CMV retinitis found that the risk of developing KS was reduced 75% and 93%, respectively, compared with an intravitreal ganciclovir implant alone (45).

Although aforementioned data are encouraging, randomized trial of using antivirals to prevent KS are lacking, the efficacy in preventing KS in persons without advanced HIV, or preventing MCD or PEL, remains unknown.

Antiretroviral therapy

Preliminary clinical reports concerning the impact of antiretroviral therapy on modifying both the incidence and clinical expression of KS are encouraging.

The risk of developing KS was reduced 26% among 1,204 HIV-positive English men who used NRTIs alone, 53% in those on HAART regimens with NNRTIs, and 58% among men taking PIs after adjustment for age, ethnicity, and nadir CD4 count before developing KS. PI- and NNRTI-based HAART regimens are equally effective as protection against KS. This is the first study to demonstrate a decreased incidence of an AIDS-defining disease with NNRTI-based therapy (60).

The large Swiss HIV Cohort Study showed that the standardized incidence ratio (SIR) for KS among HIV-positive persons was reduced nearly 10-fold for those who used HAART before developing KS (SIR

for HAART users 25.3 vs. 239 for nonusers) (15). And KS incidence fell abruptly in 1996-1998 to reach a plateau at 1.4 per 1000 py afterwards. The hazard ratios (HR) for KS declined steeply in the first months after HAART initiation and continued to be low 7-10 years afterwards (HR, 0.06; 95% CI, 0.02-0.17). Five hundred and ninety-seven incident KS cases were identified of whom 52 were among HAART users. Thirty-three out of 52 (63.5%) KS cases among HAART users arose among PWHA (people with HIV/AIDS) who had stopped treatment or used HAART for less than 6 months (22).

A study of the influence of AIDS epidemic and HAART on the incidence of Kaposi sarcoma (KS) conducted in Canada showed that KS was a rare cancer before the 1980s; however, incidence increased sharply between 1985 and 1995 by 13.8% per year. Thereafter, incidence rates fell close to those in the early 1980s. The AIDS epidemic, the introduction of antiretroviral therapies, and the decrease in HIV infection rates explain the rise and decline of KS incidence in Ontario (4).

Although the mechanisms by which ART or HAART influences the incidence rates of KS remain incompletely understood, these findings suggest that immune reconstitution may be important in preventing the occurrence of KS.

TREATMENT OF KSHV-ASSOCIATED DISEASES WITH ANTIVIRALS

Kaposi's sarcoma

Although several chemotherapeutic agents have proven effective in controlling KS, the growing understanding of its pathogenesis increasingly provides a strong rationale for using non-cytotoxic agents for treatment.

Several lines of evidence have suggested that AIDS-associated KS respond well to antiretroviral drugs. Case reports indicated that the use of PIs was associated with remission of AIDS-associated KS (18, 32, 38, 46, 51, 68). A retrospective study of 78 patients with AIDS-associated KS, HAART with either a PI or a NNRTI prolonged the time to receipt of additional topical or systemic therapy, compared with treatment courses in these same patients before initiating HAART (11). Twelve of 14 (86%) of patients previously treated with ART or chemotherapy had remissions in their KS documented at a median of 4 months after initiating PI-based ART; the clinical response was correlated with a decrease in plasma HIV-1 RNA levels and an increase in $CD4^+$ lymphocytes, whereas antibody levels to the lytic-phase KSHV protein were influenced by the extent of tumor involvement (13). KSHV viremia was also significantly reduced among persons on PIs, which was independently predictive of KS improvement (40, 59). The switching from PI-based to NNRTI-based HAART can cause relapse (5) and new onset (61) of KS. This suggests that the efficacy of different ART regimens in treating KS may be different.

Although it has been suggested that reducing the load of KSHV prior to the appearance of KS lesions may reduce the risk of developing KS (23, 49), the efficacy of DNA synthesis inhibitors in treating KS is not well established. A clinical trial was conducted to test the activity of cidofovir (CDV), a drug with *in vitro* activity against KSHV in KS. Five patients with human immunodeficiency virus-associated KS (4

receiving antiretroviral therapy) and 2 patients with classical KS were administered CDV (5 mg/kg/dose) weekly for 2 weeks and then every other week. All 7 patients had progression of their KS at a median of 8.1 weeks (range, 5-27 weeks). There was no decrease in the virus load of KSHV in peripheral blood mononuclear cells. This study does not provide proof of principle for the treatment of KS with CDV. However, it remains possible that anti-herpesvirus therapy can be developed for herpes-induced tumors (42). The hypothesis could be put forward that blocking KSHV replication may not affect existing KS lesions but may prevent new lesions from developing.

Primary effusion lymphoma

Primary Effusion Lymphoma (PEL) is a very rare subtype of non-Hodgkin's lymphoma, predominantly associated with HIV-infected individuals. The relative rarity of PEL makes definitive evaluations of its treatment challenging. Successful treatment of PEL, either alone or with adjunctive chemotherapy, immunotherapy or HAART, has been described to date with both ganciclovir (16, 57) and cidofovir (16, 28, 44). Similar results have been observed in MCD patients treated with ganciclovir (12, 69), but failures have been reported with cidofovir (8). Recent data suggests that some PEL lines are quite sensitive to inhibition of NF-kB, suggesting that inhibitors of NF-kB potentially can be developed as therapy for patients with PEL (37). Several clinical trials are currently enrolling patients to assess the efficacy of antiviral or inductive therapy in the treatment of KSHV-associated disease.

Multicentric castleman disease

Compared with other KSHV-associated diseases, MCD is characterized by active KSHV replication, and many of the symptoms of MCD may be attributable to viral gene products (33, 34). The treatment effect resulting from the direct antiviral potency against KSHV or the direct action of antiretroviral drugs on HIV known to trigger MCD is poorly defined. Clinical flares of MCD are consistently accompanied by KSHV viremia, which resolve with effective therapy (10, 24, 56). One series (12) described the effect of ganciclovir on the clinical and virologic course of MCD in a series of 3 case reports. Two patients experienced a reduction in the frequency of episodic flares of MCD and detectable KSHV DNA with intravenous or oral ganciclovir, whereas the third patient recovered from an acute episode of renal and respiratory failure with intravenous ganciclovir therapy. Two of the three patients experienced disease-free intervals of over 1 year. In contrast, another series showed that five patients with HIV-associated MCD failed to respond to the combination of cidofovir and chemotherapy (8). In antiretroviral therapy, one series suggested that the initiation of ART in three patients with MCD could lead to a fulminant and fatal course (73). The other series of seven cases suggested no relationship between ART, CD4 count, and the course of MCD (1).

SUMMARY

Since the first description of KSHV in 1994, many studies have addressed important findings in the retrospective epidemiologic studies, molecular biology, pathogenic factors and clinical observations associated with its infection. These findings suggest a role for antiviral therapy in the prevention and treatment of

KSHV-associated diseases. The therapy of KSHV-associated diseases has taken advantage of the concomitant activity against this virus with antiherpetic drugs or antiretroviral drugs. However, treatment options could be greatly improved by establishing reliable *in vitro* and *in vivo* models for studying interactions between the drug and the virus itself and for obtaining appropriate information on the pharmacokinetic and pharmacodynamic properties of novel anti-KSHV drugs. In view of the fact that HAART is more efficient than double or single antiretroviral drugs in reducing KS risk, it is conceivable that new and affordable antiretroviral drugs are needed. This is especially true in the developing countries, such as sub-Saharan Africa, where AIDS-KS remains a major problem. Recent basic research identified several new targets for potential future therapies, including inhibitors of viral replication, cell signaling, inflammation and angiogenesis. Great progress in chemotherapy has been made in the past decade to target specific molecules involved in oncogenesis. Clinical trials to evaluate the efficacy using combination of different antiviral therapy and chemotherapy may need to be established.

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