Anti-herpesvirus treatment and risk of Kaposi’s sarcoma in HIV infection

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Objective: With the recent identification of a new herpesvirus in patients with Kaposi’s sarcoma (human herpesvirus-8 or Kaposi’s sarcoma-associated herpesvirus), there have been several reports on the use of anti-herpesvirus therapy (foscarnet, ganciclovir and aciclovir) and risk of developing Kaposi’s sarcoma. We therefore investigated the association between use of anti-herpesvirus drugs and Kaposi’s sarcoma in a large unselected group of patients with AIDS.

Patients and methods: We studied a group of HIV-positive patients at the Chelsea and Westminster Hospital, for whom details on all AIDS-defining diagnoses made during follow-up, treatment and regular CD4 counts were available. Cox proportional hazards models with time-dependent covariates were used to assess the association between treatment with aciclovir, foscarnet and ganciclovir and risk of Kaposi’s sarcoma.

Results: A total of 3688 patients have been followed up for a median period of 4.2 years, during which time 598 patients (16.2%) developed Kaposi’s sarcoma. After adjustments for sex, exposure category, age, treatment with antiretrovirals or Pneumocystis carinii pneumonia prophylaxis, the development of AIDS-defining conditions (including separate adjustment for the development of cytomegalovirus and herpes simplex virus) and CD4 count; there was a decreased risk of developing Kaposi’s sarcoma with foscarnet [relative hazard (RH), 0.38; 95% confidence interval (CI); 0.15–0.95; P = 0.038] and with ganciclovir (RH, 0.39; 95% CI, 0.19–0.84; P = 0.015), but not with aciclovir (RH, 1.10; 95% CI, 0.88–1.38; P = 0.40).

Conclusions: These results suggest that both foscarnet and ganciclovir may have some activity in preventing the occurrence of Kaposi’s sarcoma, but that aciclovir has no benefit. Further studies of the effect of these drugs on the risk of Kaposi’s sarcoma is warranted.

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Keywords: Kaposi’s sarcoma, disease progression, foscarnet, ganciclovir, aciclovir

Introduction

Kaposi’s sarcoma (KS) was first described by Moritz Kaposi, a Hungarian dermatologist, in 1872, and in its classical form this rare lesion appears as a pigmented sarcoma usually appearing on the lower legs of predominantly older Jewish and Eastern European men [1]. In 1980, the first cases of KS in young homosexual men heralded the arrival of AIDS-associated KS [2]. In contrast to classical KS, AIDS-associated KS has an aggres-
The identification of a new herpesvirus [human herpesvirus-8 or KS-associated herpesvirus (KSHV)] as a possible causal factor in the development of KS [4-7] has led to analyses aimed at assessing whether the use of drugs active against herpesviruses can prevent the development of KS. Jones et al. [8] used a Cox proportional hazards model to determine the association between aciclovir, ganciclovir and foscarnet and the subsequent risk of KS in a large US follow-up study based on medical records. They found a significantly reduced risk of developing KS associated with the use of foscarnet, but not with aciclovir or ganciclovir, after adjustment for CD4 lymphocyte count, age, race, sex, exposure group, other AIDS opportunistic illnesses and antiretroviral treatment. In contrast, a similar analysis from France found no reduced risk with any of the three drugs [9]. Surprisingly, both studies found a significantly increased risk of KS associated with the use of aciclovir. A further study from the Multicentre AIDS Cohort Study found a reduced risk of KS among patients treated with foscarnet or ganciclovir, but the result was not significant [10].

In this study, we provide further evidence on this important issue with an analysis of the risk of KS among 3688 patients followed at the Chelsea and Westminster Hospital in London. We also identify several issues relating to the way in which the analysis is performed which could help to explain apparent inconsistencies with and between the previous studies.

Patients and methods

Patients
All HIV-positive patients seen at the Chelsea and Westminster Hospital between July 1985 and 31 July 1995 (the cut-off date for this analysis) were included in this study if they did not have a diagnosis of KS either at their initial visit or within 1 month of this first visit. AIDS was diagnosed according to the classification in use at the time, and thus patients have not been retrospectively diagnosed with AIDS. Diagnoses made after 1993 are diagnosed according to the 1993 revised clinical criteria from the Centers for Disease Control and Prevention [11]. Patients with no clinical diagnosis and a CD4 lymphocyte count of below 200 x 10^6/l are not included as AIDS patients. Demographic data, clinical events and treatment are recorded and maintained on a database system which is regularly updated. Dates of stopping treatment are not recorded and all analyses presented consider only whether a patient has ever started treatment, consistent with an intention-to-treat analysis. CD4 counts were measured at regular intervals on these patients and added to the database.

Treatment policies
Currently, no patients are offered primary prophylaxis for cytomegalovirus (CMV). Patients with diagnosed CMV syndromes are treated with foscarnet 90 mg/kg twice daily for 14–21 days or ganciclovir 5 mg/kg twice daily. Treatment for gastrointestinal CMV disease is stopped once a patient has recovered, but secondary prophylaxis is usually given for CMV retinitis with foscarnet 90 mg/kg once daily, or with ganciclovir 5 mg/kg once daily, 5–7 days per week. From 1994, patients have been given 1 g oral ganciclovir daily for secondary prophylaxis. All patients with recurrent herpes infections are treated with aciclovir 400 mg twice daily and all patients are offered aciclovir 400 mg twice daily when their CD4 cell count drops below 100 x 10^6/l, as a possible effect on the suppression of herpesviruses may occur [12]. Patients who participated in a primary prophylaxis study of high-dose aciclovir were given the option of remaining on the study medication.

Statistical methods
A Cox proportional hazards model was used to assess the association between the use of aciclovir, foscarnet and ganciclovir and the risk of developing KS. The survival time for each patient was measured as the time from their initial visit to the Chelsea and Westminster Hospital until the development of the first KS lesion, last patient visit, death, or 31 July 1995, whichever occurred first. Treatment with aciclovir, ganciclovir and foscarnet, together with antiretrovirals and Pneumocystis carinii pneumonia (PCP) prophylaxis, was fitted as a time-dependent covariate taking the value '0' until a patient started treatment and remaining at '1' thereafter. The CD4 lymphocyte count was also fitted as a time-dependent covariate. In common with previous analyses with AIDS as endpoint [13,14], it was found that a logarithmic transformation of the CD4 lymphocyte count provided a better fitting model. We also adjusted for the occurrence of other AIDS-associated illnesses. In particular, the occurrence of CMV disease or herpes simplex virus (HSV) disease were fitted separately, again as time-dependent covariates, taking the value '0' before the occurrence of disease and '1' thereafter.

All analyses were performed using SAS statistical software [15]. Tests of the significance of the variables included in the Cox proportional hazard models were performed using the Wald test. Tests of the proportional hazards assumption found no evidence of non-proportionality.

Results
A total of 3688 patients have been followed up for a median period of 4.2 years (range, 0.1–10.0 years), during which time 598 patients (16.2%) developed KS. CMV disease was diagnosed in 510 patients (13.8%). Of these, 296 patients were diagnosed with retinitis, 324...
patients were diagnosed with gastrointestinal disease, and 110 patients had a diagnosis of both. A much smaller number of patients were diagnosed with HSV: 46 patients (1.2%). The majority of the patients were men (n = 3487; 94.5%) and homosexual or bisexual (n = 3409; 92.4%). The median age at first visit was 30.2 years (range, 14.6–67.3 years), and the men were significantly older than the women (median ages of 30.4 and 27.1 years, respectively; P < 0.0001, Wilcoxon). The median CD4 count at initial visit was 288x10^6/μl (range, 0–2520x10^6/μl), which did not vary significantly according to sex or exposure category. During follow-up, 2349 patients (63.7%) had at least one CD4 lymphocyte count below 200x10^6/μl, 1899 (51.5%) started PCP prophylaxis during follow-up, 1650 patients (44.7%) were treated with aciclovir, 132 (3.6%) were treated with foscarnet but not ganciclovir, 201 (5.5%) with ganciclovir but not foscarnet, and 77 patients (2.1%) were treated with both ganciclovir and foscarnet. Generally, patients were treated with aciclovir at an earlier stage before treatment with either ganciclovir or foscarnet began. Seventeen patients took foscarnet before aciclovir, and 16 patients took ganciclovir before aciclovir. A large proportion of patients were also treated with antiretrovirals and PCP prophylaxis; 1930 patients (52.3%) were treated with antiretrovirals and PCP prophylaxis which did not vary significantly according to sex or exposure category. During follow-up, 2349 patients (63.7%) had at least one CD4 lymphocyte count below 200x10^6/μl, 1899 (51.5%) had a CD4 count below 50x10^6/μl and 1592 (43.2%) had a CD4 count below 50x10^6/μl.

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Table 1 shows the relative hazard (R.H) of developing KS associated with each of the three anti-herpesvirus drugs, along with CD4 lymphocyte count, use of antiretroviral therapy and PCP prophylaxis, race, age, exposure group, sex, previous CMV disease, previous HSV disease and any other previous AIDS-defining diseases. The R.H are shown with and without mutual adjustment. After adjustment, it can be clearly seen that treatment with either foscarnet (R.H, 0.38; 95% confidence interval (CI), 0.15–0.95) or ganciclovir (R.H, 0.39; 95% CI, 0.19–0.84) was associated with a significantly lower risk of subsequently developing KS. A low CD4 count was, as expected, strongly associated with the risk of KS.

These analyses were repeated considering only homosexual and bisexual men, and only considering patients who were first seen after 1990 when the methods used for the collection of routine data such as these were changed. Analyses were also repeated excluding patients who were seen prior to foscarnet becoming available in 1987 and the launch of ganciclovir in October 1988, and by separately modelling CMV gastrointestinal disease and CMV retinitis, which may involve different lengths of treatment. In all cases results were similar to those presented above (data not shown).

Although not all patients who developed CMV disease were treated, foscarnet and ganciclovir were highly correlated with CMV disease, which may lead to a problem of multicollinearity. This occurs when the model cannot separately estimate the effect of treatment with foscarnet and ganciclovir and the development of CMV disease, because they are highly correlated. To address this problem, we looked at the risk of developing KS after treatment with ganciclovir or foscarnet (modelled as a single variable). We adjusted for the development of AIDS as a time-dependent covariate, but with no separate adjustment for CMV disease. The relative risk of developing KS associated with treatment in this model was 0.39 (95% CI, 0.20–0.73; P = 0.004).

A further issue was that patients who reach a certain stage of HIV disease may no longer be at risk of developing KS. For example, it may be that a patient infected with KSHV will develop KS at a particular level of immunodeficiency. If KS does not develop during patient follow-up it may indicate that this patient was not infected with KSHV. This scenario was extremely unlikely given that the risk of developing KS continued to increase as the CD4 lymphocyte count decreased (Table 1). A further model, which included the untrans-
formed CD4 lymphocyte count as a time-dependent categorical variable (> 200, 101–200, 51–100 and ≤ 50×10^6/l), showed that the risk of KS in patients with a CD4 count of 50×10^6/l or less was over twice that of patients with a CD4 count of 51–100×10^6/l (RH, 2.11; 95% CI, 1.66–2.70; P = 0.0001). As in the other models, treatment with either foscarnet or ganciclovir was associated with a significantly reduced risk of KS (RH, 0.39; 95% CI, 0.21–0.75; P = 0.005).

Table 2. The relative hazard of Kaposi’s sarcoma associated with the use of anti-herpesvirus therapy: an alternative modelling strategy.

<table>
<thead>
<tr>
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<th>RH (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (10-year increase)</td>
<td>0.96 (0.86–1.08)</td>
<td>0.51</td>
</tr>
<tr>
<td>Female</td>
<td>0.10 (0.02–0.52)</td>
<td>0.0037</td>
</tr>
<tr>
<td>Homo-/bisexual</td>
<td>1.15 (0.51–2.59)</td>
<td>0.73</td>
</tr>
<tr>
<td>AIDS diagnosis</td>
<td>1.44 (1.14–1.75)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Antiretroviral treatment</td>
<td>0.86 (0.63–1.17)</td>
<td>0.18</td>
</tr>
<tr>
<td>PCP prophylaxis</td>
<td>1.14 (0.89–1.45)</td>
<td>0.31</td>
</tr>
<tr>
<td>CD4 count*</td>
<td>1.71 (1.58–1.86)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>1.21 (0.96–1.51)</td>
<td>0.11</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>0.54 (0.22–1.35)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>0.68 (0.33–1.40)</td>
<td>0.29</td>
</tr>
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*Relative hazard is per 100×10^6/l drop in CD4 count. RH, Relative hazard; CI, confidence interval; PCP, Pneumocystis carinii pneumonia.

We also repeated our main analysis without adjusting for CMV and HSV disease separately from other diseases and fitting the unlogged CD4 count to investigate the extent to which these changes in the modelling process could alter the results. All variables, with the exception of sex, age and exposure category, were fitted as time-dependent covariates in the same way as described above. The adjusted RH are shown in Table 2. Here, the RH of the CD4 count can be interpreted as the risk of developing KS associated with each 100×10^6/l drop in the CD4 count after adjustment for all other variables. Using this alternative model would appreciably alter our conclusions; foscarnet and ganciclovir are associated with a lower risk of developing KS (RH, 0.54 and 0.68, respectively), but the result is no longer significant.

Discussion

Results from this analysis suggest that both foscarnet and ganciclovir may have activity in preventing the occurrence of KS in HIV infection, but that aciclovir has no effect. Our findings on foscarnet are consistent with those from Jones et al. [8] who found a RH of 0.3 (95% CI, 0.1–0.6), but not with those from Costagliola et al. [9] who obtained a RH of 1.36 (95% CI, 0.40–2.37). In contrast to our study, both studies found no association between ganciclovir use and risk of KS. The differences in results from different studies may lie, in part, in the way in which the analysis was performed. All three studies have followed patients with a wide initial range of CD4 count, the presence of CMV, HSV or any other AIDS diagnosis is naturally positively associated with a higher risk of KS, since they tend to occur at low CD4 counts [16]. This means that foscarnet and ganciclovir use are associated with a raised risk of KS, as can be seen in the univariate analysis in Table 1. The multivariate analysis attempts to remove this confounding due to disease stage by adjusting for the patients’ stage of disease through the CD4 lymphocyte count and diagnosis of AIDS-defining diseases. After this adjustment in our analysis the potential preventive effect of the therapy was revealed. If the adjustment for stage of disease is inadequate, then this potential preventive effect would remain masked. The analysis in Table 2 indicates how an analysis where the CD4 count was fitted as an unlogged variable and CMV and HSV diseases were not fitted separately leads to estimates of treatment effects closer to one (i.e., no effect). The reduced RH shown in Table 2 are consistent with those of Glesby et al. [10], who showed a non-significant reduction in risk of 0.56 with ganciclovir (95% CI, 0.22–1.44) and 0.40 with foscarnet (95% CI, 0.05–3.10). Given the brevity of reports from the other studies, it is not possible to tell how much these considerations could affect their findings [9,10].

Our study has the benefit of a considerably longer follow-up period, and that the dates of all AIDS-defining illnesses and treatment were routinely recorded. All the patients were cared for at a single institution, so treatment policies and access to care were relatively uniform. Our findings of a reduced risk of KS after treatment with foscarnet and ganciclovir, both anti-herpesvirus treatments, add weight to the argument that a human herpesvirus is associated with the development of KS. We found no reduced risk of KS in patients who were treated with aciclovir, and this may be due in part to the routine use of aciclovir to treat recurrent herpes infections and subsequent resistance.

In conclusion, our study has shown that patients treated with either foscarnet or ganciclovir are at a reduced risk for the development of KS. There is a potential for confounding of treatment and disease, because patients who develop CMV disease are likely to be those who are treated with ganciclovir or foscarnet. However, for this confounding to explain our findings, those patients with CMV disease would have to be at a lower risk of KS compared with those patients without CMV disease but with similar CD4 lymphocyte counts. In addition, it should be remembered that this study was retrospective and not one of randomized treatments, and thus lacks the power that a randomized study of anti-herpesvirus treatment would have. As Costagliola et al. [9] remind us, none of these analyses are of randomized comparisons, so caution is required in their interpretation.
References


Appendix

Members of the Royal Free/Chelsea and Westminster Collaborative Group
