Failure of cidofovir in HIV-associated multicentric Castleman disease

Multicentric Castleman disease (MCD) is a distinct lymphoproliferative disorder characterized by lymphadenopathy with angiofollicular hyperplasia and plasma cell infiltration. Patients typically have fever associated with lymphadenopathy, hepatosplenomegaly, respiratory symptoms, peripheral edema, cytopenia, hypergammaglobulinemia, hypoalbuminemia, and high levels of serum C reactive protein (CRP). In the context of HIV infection, MCD is associated with Kaposi sarcoma–associated herpesvirus (KSHV). Clinical symptoms correlate with an important increase of KSHV DNA in peripheral blood mononuclear cells (PBMCs). Vinca alkaloids produce frequent but short-lived responses, and most patients remain dependent upon chemotherapy. Rituximab has been reported to be effective. Besides cellular targets, viral targets could be considered for intervention. In vitro, KSHV replication can be inhibited by some antiviral drugs such as ganciclovir, foscarnet, and cidofovir.

We have read with interest the article by Casper et al on the treatment of HIV-associated MCD with ganciclovir. This study, showing a response to ganciclovir in 3 patients, suggested that antiviral agents against KSHV could be used in the management of MCD. However, clinical remission was short lived for patient 2, and patient 1 died with fungal infection after 12 days of ganciclovir. Only the third patient had a long-lasting remission after a 21-day course of valganciclovir. Clinical symptoms were correlated with high serum CRP values. In contrast, our experience with cidofovir could be considered for intervention. In vitro, KSHV replication can be inhibited by some antiviral drugs such as ganciclovir, foscarnet, and cidofovir.

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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. CD4 T cells, × 10^9/L</th>
<th>KS Delay from MCD, diagnosis, mo</th>
<th>Current therapy for MCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>320</td>
<td>+</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>109</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>701</td>
<td>+</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>259</td>
<td>+</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>584</td>
<td>–</td>
<td>24</td>
</tr>
</tbody>
</table>

KS denotes Kaposi sarcoma; MCD, multicentric Castleman disease.

Patients received 3 to 6 CDV infusions over 21 to 60 days. All 5 patients experienced repeated recurrence of MCD symptoms during the study and remained dependent upon chemotherapy. Clinical symptoms were correlated with high serum CRP values and high KSHV copy numbers in PBMCs without any demonstrable impact of cidofovir on these parameters. Patient 5 had no response with an increase of KSHV DNA in PBMCs and was splenectomized, as a diagnosis of lymphoma was suspected. The treatment was prematurely interrupted in 4 patients because of evident failure (Figure 1).

Anecdotal reports of Kaposi sarcoma (KS) responding to antiviral drugs and studies showing that treatment of AIDS patients with ganciclovir or foscarnet for cytomegalovirus disease reduced the risk of KS could suggest that antiviruses drugs might be effective against KSHV-associated diseases. Moreover, MCD differs from KS not only in the infected cell type, but also in the pattern of viral gene expression as infected cells from MCD express both latent and lytic proteins. This point could argue for a possible direct efficacy of antiviral drugs in KSHV-associated multicentric Castleman disease. However, the pathologic features, the frequent evolution of MCD toward KSHV non-Hodgkin lymphoma, the failure of CDV, and the effectiveness of chemotherapy and rituximab suggest that the profile of this disease remains closer to that of a virus-associated lymphoproliferative disorder.

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To the editor:

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References


Response:

The role of antiviral agents in the treatment of multicentric Castleman disease

We appreciate the interest in our article, “Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment,” and the thoughtful description of 5 patients with multicentric Castleman disease (MCD) by Berezne et al. Their letter characterizes 5 patients with “chemo-dependent” MCD and shows that neither treatment with vinblastine, etoposide, or cidofovir, nor splenectomy, was effective in reducing the frequent flares of MCD.

Of the findings, 2 appeared similar between our study and that of Berezne et al. First, it is notable that the treatment of patient 2 with etoposide had negligible effects, as we observed with 1 patient in our series. Additionally, as first described by Oksenhendler et al, both studies found that remission of clinical symptoms is consistently accompanied by declines in human herpesvirus 8 (HHV-8) viremia, although causality is difficult to infer.

As the pathogenesis of MCD is unclear, especially its relationship to ongoing HHV-8 replication, the role antivirals play in inducing remissions is unknown. The mechanism of viral inhibition is likely to influence the efficacy of an antiviral drug. Ganciclovir and cidofovir both inhibit the secretion of HHV-8 virions after stimulation of latently infected immortalized cells. In one study, however, cidofovir failed to block the production of early-lytic HHV-8 antigens.

Our study and the cases described by Berezne et al illustrate the need to evaluate HHV-8 replication in HHV-8- and HIV-associated MCD. Controlled trials of therapies of this infection are warranted and are the best way to define what will emerge as the optimal treatment.

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References


To the editor:

Only genuine CD4+CD25+ Tregs may be friends or foes

In their recent paper, Stanzani et al sought to ascertain whether the relationship between donor CD4+CD25+ regulatory T cells (Tregs) and graft-versus-host disease (GVHD) severity, found in murine transplantation, would hold up in humans. With this aim, they measured CD4+ and CD8+ T cells coexpressing CD25 within 60 donor grafts infused into matched siblings, reaching the unexpected conclusion that higher numbers of donor CD4+CD25+ (as well as CD8+CD25+) T cells correlated with an increased risk for GVHD. A similar association was stated for the CD4+CD25 high subset, but data were not shown. Thus, it was clear that authors referred to Tregs.

If we had thought to demonstrate a similar hypothesis, we would have tried to more appropriately identify the subset of CD4+CD25+ Tregs. As stated by the authors, we agree that currently no surface molecules are known as truly specific for Tregs and, in accordance with convention, the intensity of CD25 expression on CD4+ T cells is used to point out Tregs but CD25 expression may be induced potently and persistently by several stimuli on conventional T cells. Consequently, the lack of expression of a phenotype of recently activated T cells should be always assessed on presumed Tregs subset. Indeed, isolated murine and human CD4+CD25+ Tregs are known to be hyporesponsive to alloimmune or polyclonal activation, to suppress the proliferation and cytokine secretion by activated CD4+CD25+ responder T cells, and to express Foxp3, as recently demonstrated in both murine and human Tregs.

Almost all papers so far published, except that of Stanzani et al, following the identification of a population of nonactivated CD4+CD25+ T cells, provide in vitro evidence that these cells are endowed with immunoregulatory properties. Taking this into consideration, we, and likely all people working with Tregs, agree with the authors’ sentence asserting that “...the coexpression of CD4 and CD25 may be insufficient to identify regulatory T cells in humans.” But, whether...
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