Potent Inhibition of Hemangioma Formation in Rats by the Acyclic Nucleoside Phosphonate Analogue Cidofovir

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ABSTRACT

The acyclic nucleoside phosphonate analogue cidofovir elicited a marked protection against hemangioma growth in newborn rats that had been infected i.p. with a high titer of murine polyomavirus. Untreated, infected rats developed cutaneous, i.m., and cerebral hemangiomas associated with severe hemorrhage and anemia leading to death within 3 weeks postinfection (p.i.). s.c. treatment with cidofovir at 25 mg/kg, once a week, resulted in a complete suppression of hemangioma development and associated mortality when treatment was initiated at 3 days p.i. (100% survival compared with 0% for the untreated animals). Cidofovir still afforded 40% survival and a significant delay in tumor-associated mortality when treatment was started at a time at which cerebral hemangiomas were already macroscopically visible (i.e., 9 days p.i.). Infectious virus or viral DNA was undetectable in the brain at different times p.i. as assessed by means of (a) a DNA-DNA hybridization assay and (b) titration of the brain for infectious virus content, indicating that there was no viral replication in murine polyomavirus-infected rats. Moreover, a semiquantitative PCR for viral protein 1 DNA revealed that the amount of viral protein 1 DNA declined with time after infection to become virtually undetectable at 18 days p.i. Therefore, an antitumor or antiangiogenic effect, rather than inhibition of viral replication, may be the reason for the inhibitory activity of cidofovir in this model. Cidofovir may thus be further explored for the treatment of vascular tumors and, in particular, life-threatening juvenile hemangiomas.

INTRODUCTION

Hemangiomas are benign, endothelial tumors that occur in 10% of all newborns and in up to 22% of preterm babies weighing <1 kg. In contrast to vascular malformations, hemangiomas are not present at birth. However, they appear shortly postpartum and continue to grow very rapidly for the following 6 months. This proliferative phase is generally followed by regression of the tumor during the next 5–10 years (1). Approximately 10% of the tumors do not resolve completely, and 3–5% become extremely large, involve vital organs, and can cause life-threatening complications, such as ulceration, infection, hemorrhages, and Kasabach-Merritt syndrome, which may be fatal when left untreated. Treatment with steroids has been recommended for these alarming hemangiomas. However, the response rate has been variable, and complications have occurred frequently (2). Radiation therapy is no longer used because of its malignant potential, and surgical therapy (resection or arterial ligation) is only performed as a last resort when other therapies have failed (3, 4).

In 1987, Folkman and Klagsbrun (5) put forward the concept of “angiogenic diseases,” which are characterized by abnormal, unregulated capillary growth. Examples of diseases in which formation of blood vessels is no longer under stringent control include diabetic retinopathy, psoriasis, and hemangiomas (6). Therefore, antiangiogenic therapy could improve the life span of hemangioma-bearing children. At present, IFN-α is being used with relative success for the treatment of hemangiomas (7, 8). The mechanism underlying this antitumor action is, however, not completely understood.

We have developed a novel animal model for the study of strategies for the treatment of hemangiomas. Infection of newborn rats with a high titer of the Marseille strain of mPyV(3) was found to induce cutaneous, i.m., and intracerebral hemangiomas with a short latency period. The cerebral hemangiomas were associated with hemorrhage, resulting in severe anemia and subsequent death of the animals within 3 weeks postinfection (p.i.). Because newborn animals are used in this model, only selective inhibitors with low toxicity may cause protection. This model may thus be relevant to the pediatric clinical setting and suitable for the preclinical evaluation of strategies for the treatment of this disease.

Cidofovir is an acyclic nucleoside phosphonate analogue with broad-spectrum antiviral activity (9, 10), which has been approved in the United States and Europe for the treatment of cytomegalovirus retinitis in AIDS patients. Cidofovir has also been found to induce regression after topical treatment of severe, relapsing penile, perigenital-intra-anal, and cervical/vulvar lesions associated with HPV (11). Furthermore, we have recently shown that cidofovir also has potent antitumoral activity against NPCs that were grown in athymic, nude mice (12).

The present study was designed to evaluate the growth of hemangiomas and, therewith, associated mortality in rats after systemic treatment with cidofovir at clinically achievable doses (13).

MATERIALS AND METHODS

Animals. Rats of the inbred Wistar R strain were used throughout the experiments. The rats were obtained from the Animal Production Center of the Katholieke Universiteit Leuven and were housed under germ-free conditions during the experiments.

Virus. mPyV (strain Marseille) was grown in MEF cultures and titrated with the plaque method of Dulbecco and Freeman in MEF cells as described before (14).

Cells. UC1-B cells (MEFs, ATCC 6465-CRL) and MO cells (murine C3H3T; fibroblasts) were used. Cells were grown in MEM supplemented with 10% inactivated FCS, 1% l-glutamine, and 1% sodium bicarbonate.

Animal Studies. Four-day-old rats were infected i.p. with either 10⁵.7 or 10⁷ pfu of mPyV. Cidofovir ([5]-3-hydroxy-2-phosphonylmethoxypropyl) cytosine), kindly provided by Gilead Sciences, Foster City, CA was injected s.c. in 200 μl of MEM, according to a variety of treatment schedules, as described in “Results.” Control animals received the same volume of MEM only. Mortality and the appearance of cutaneous hemangiomas were recorded daily for those rats that were infected with 10⁷ pfu. Those animals that had been infected with 10⁷ pfu were killed at 4 weeks p.i. The brains, lungs, liver, spleen, and kidneys were dissected and fixed in Bouin’s fluid and embedded in paraffin, and sections were stained with H&E.

Statistical Analysis. The two-tailed unpaired Student’s t test was used to calculate the differences in the MDD and in the mean lesion score. Statistical significance of differences in the number of rats with cerebral hemangiomas was evaluated by the χ² test with Yates’ correction.

The abbreviations used are: mPyV, murine polyomavirus; HPV, human papillomavirus; MDD, mean day of death; MEF, murine embryo fibroblast; NPC, nasopharyngeal carcinoma; p.i., postinfection; VP1, viral protein 1; pfu, plaque-forming unit.

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Dissection and Processing of Organs. Four-day-old rats were infected i.p. with $10^9$ pfu of mPyV. At different time points after infection (i.e., 4 h or 3, 6, 9, 12, 15, or 18 days p.i.), animals ($n = 2$) were dissected aseptically, each time using clean scissors and forceps. A parallel group of infected animals received s.c. treatment with cidofovir (25 mg/kg, once a week), starting at 3 days p.i. These animals were killed at 6, 9, 12, 15, or 18 days p.i., and brain, lungs, liver, kidney, and spleen were removed. Individual organs were homogenized through a 70-μm nylon cell strainer (Becton Dickinson, Vel, Leuven, Belgium) and were suspended (10% w/v) in MEM containing 2% FCS. Total DNA was purified from these tissue suspensions by the QIAamp Tissue Kit (Qiagen, Westburg, Leusden, the Netherlands).

Determination of VP1 DNA Levels in Different Organs. A semiquantitative PCR was used to detect the presence of VP1 DNA in the different organs. The following primers (Gibco, Merelbeke, Belgium) were used for detection of VP1: 5’-GAA AAA GCG GCG TCT CTA AAT G-3’ and 5’-ACC CCT TCT TCT TCT GTC-3’. To make quantification of the PCR products possible, dilutions of the virus stock were made, and PCR products obtained after different cycles were run on the gel to define the number of cycles required to obtain a concentration-dependent response (below saturation level). All PCR reactions were performed using Taq Polymerase (Sphaero Q, Leiden, the Netherlands). For amplification of VP1 DNA, the following program was run for 28 cycles: denaturation, 94°C, 45 s; annealing, 57°C, 45 s; and extension, 72°C, 1 min.

Determination of the Virus Titers in Brain, Lungs, and Spleen of mPyV-infected Rats. Titrations of tissue homogenates using 10-fold dilutions were performed on confluent UC1-B and MO cells grown in 24-well microtiter plates. The virus stock was used as a positive control. After a 2-h incubation period, residual virus was removed, and the infected cells were further incubated with MEM supplemented with 2% inactivated FCS, 1% L-glutamine, and 1% sodium bicarbonate. After 5 days of incubation at 37°C, the virus-induced cytopathic effect was monitored microscopically.

Dot Blot Assay. Five micrograms of denaturated DNA extracted from brains of control and cidofovir-treated animals (dissected at different times p.i. with mPyV) and serial dilutions of denaturated total cellular DNA, obtained from mPyV-infected MO cell cultures (as positive control), were blotted onto a nylon membrane (Hybond-N, Amersham). Subsequently, DNA was UV cross-linked, after which prehybridization was performed for 1 h at 42°C. The VP1 probe was labeled with digoxigenin-dUTP in a PCR. The probe was gel purified, and hybridization was performed for 18 h at 42°C with 30 ng/ml digoxigenin-11-dUTP-labeled probe. The membrane was washed at high stringency [2× SSC (1× SSC is 0.15 M NaCl plus 0.015 M sodium citrate) and 0.1% SDS] for 10 min at room temperature, followed by two washes of 15 min.
INHIBITION OF HEMANGIOMA GROWTH BY CIDOFOVIR

RESULTS

Effect of Cidofovir on Tumor Incidence and Associated Mortality after Infection of Rats with a High Virus Load. i.p. infection of 4-day-old rats with \(10^5\) pfu of mPyV resulted in the development of cerebral hemangiomas that appeared macroscopically at 9 days p.i., followed by the appearance of cutaneous, i.m., and peritoneal hemangiomas at 14 days p.i. Rapid growth of the cerebral hemangiomas associated with severe hemorrhages and anemia resulted in death of the rats within 3 weeks p.i. When treatment with cidofovir (25 mg/kg, s.c., once a week) was initiated at 3, 6, or 9 days p.i., a complete (days 3 and 9) or almost complete (day 6) suppression of development of cutaneous lesions was observed (Fig. 1). Furthermore, all animals in which treatment was initiated at 3 days p.i. survived, and 25 or 40% survival was observed when treatment was initiated at 6 or 9 days p.i., respectively (Figs. 2 and 3). Survivors were kept for 6 months, at which time autopsy (and histological examination) revealed that the animals were tumor free.

A marked delay in tumor-associated mortality was observed for those animals in the day 6 and day 9 group that ultimately succumbed [i.e., MDD, 23.0 ± 3.8 for the control group compared with 37.7 ± 4.4 (\(P < 0.0005\)) and 28.0 ± 1.0 (\(P < 0.005\)) for the day 6 and day 9 group, respectively (Fig. 2)]. Even at a dose as low as 5 mg/kg once a week, s.c. treatment with cidofovir resulted in a marked protection (i.e., delay in mortality; Fig. 4). When the start of treatment was delayed until 9 days p.i., at which time cerebral hemangiomas were already clearly visible (as determined after dissection of a parallel control group), a dose of 5 mg/kg cidofovir once weekly still caused a 3-day delay in tumor-associated mortality (MDD, 23.2 ± 1.8 compared with 18.5 ± 0.6 for the control group; \(P < 0.05\)). Furthermore, although hemangiomas were observed in the brains of those animals that succumbed after this delayed low-dose cidofovir therapy, their number was markedly lower than in the control animals, and almost no hemorrhages were noted in the brains of the treated animals.

Effect of Cidofovir on Incidence and Development of Hemangiomas. To study the effect of cidofovir in a less-aggressive model for cerebral hemangiomas, 4-day-old rats were infected with a 10-fold lower virus load than was the case for the mortality experiments described above. In rats inoculated with this lower virus dose, cerebral hemangiomas developed within 14 days p.i., and cutaneous or i.m. lesions were not observed. Treatment with cidofovir (25 mg/kg, s.c., once a week) was started at different times after infection, and all animals were killed at 4 weeks p.i. Their organs (brain, lungs, kidneys, spleen, and liver) were examined macroscopically and histologically for the appearance of hemangiomas. Macroscopically detectable cerebral hemangiomas were observed in all control animals. No hemangiomas or other tumors were detectable in any of the other organs. Cidofovir therapy, started before the appearance of brain tumors (as revealed by the dissection of a parallel group of control rats at different days p.i.), inhibited the incidence of hemangiomas; i.e., compared with 100% in the control group, none of the rats developed cerebral hemangiomas when treatment was started at 3 days p.i. and only 44% of the rats developed cerebral hemangiomas when treatment was started at 9 days p.i. (Table 1). In addition, cidofovir was found to cause stabilization or even regression of already established hemangiomas. Indeed, cidofovir treatment, initiated at 14 days p.i. (at a time when brain lesions were detectable in the parallel control group), each in 0.1 \(\times\) SSC and 0.1% SDS at 65°C. After incubation in blocking buffer, the filter was incubated with an anti-digoxigenin antibody conjugated with alkaline phosphatase (anti-digoxigenin-AP and Fab fragments; Boehringer Mannheim). Detection by means of chemoluminescence was performed by standard methods.

Fig. 3. Macroscopic view of cerebral hemangiomas at 18 days p.i., after infection of newborn rats with \(10^5\) pfu of mPyV (a). Cidofovir treatment, initiated at 9 days (b) or 6 days (c) p.i., resulted in a significant decrease in number and size of the cerebral hemangiomas, whereas treatment started at 3 days p.i. completely protected against formation of the lesions (data not shown).
resulted in significantly fewer hemangiomas, which were smaller, than the control tumors (Table 1).

**Histopathology.** Tumors had the histopathological features consistent with cavernous hemangioma, showing large, blood-filled spaces lined by endothelial cells and the presence of hemosiderin-containing macrophages (Fig. 5).

**Effect of Cidofovir on Body Weight.** The effect of cidofovir (25 mg/kg, s.c., once a week) on the growth of uninfected rats was examined. Administration of the compound resulted in a minor delay in body weight gain (body weight of the cidofovir-treated animals at the end of the experiment was 88% of that of the control animals), when treatment was initiated at the age of 7 days (this would be 3 days p.i. in the virus challenge experiments). This delay was less pronounced when treatment was started at a later age or when a dose of 5 mg/kg was used (data not shown).

**Detection of Viral DNA in Different Organs.** It has been shown that mPyV causes an abortive infection in rats; i.e., little, if any, replicative virus is produced (14). To confirm these findings, a titration for infectious virus, of tissue homogenates from brains dissected at different times p.i., was performed. No infectious virus could be detected in any of these organs (data not shown). Next, a dot blot DNA-DNA hybridization assay was performed using target DNA extracted from the brains of both control and cidofovir-treated animals (dissected at different times p.i.). This method revealed that there was no detectable viral VP1 (i.e., viral capsid protein, which is produced in a lytic virus infection) DNA. In contrast, VP1 DNA was readily detectable in 1 ng of total cellular DNA extracted from mPyV-infected MO cell cultures (data not shown). Therefore, the amount of viral DNA in 25 mg of brain tissue must be well <1 ng, indicating that there is no, or no detectable, viral replication taking place. In addition, a semiquantitative PCR for VP1 was performed on brain, lungs, liver, spleen, and kidney, collected at different times after infection (Fig. 6). Serial 10-fold dilutions of the virus stock were used as standards. The amount of VP1 DNA decreased with time after infection, and, with the exception of the brain, in which a weak signal was still detectable 18 days p.i., no signal was obtained in the other organs collected at 18 days p.i. As in the untreated animals, a comparable decrease in VP1 DNA load over time was detected in the organs of those rats that had been treated with cidofovir; i.e., at 18 days p.i., only a weak signal could be observed in spleen and lungs.

**DISCUSSION**

Neoplastic processes can directly affect the cellular components of the vessel wall, giving rise to hemangiomas, hemangiosarcomas, and Kaposi’s sarcoma. Hemangiomas are benign, vascular tumors characterized by an increased endothelial cell turnover. They appear shortly after birth in 10% of all newborns and tend to regress spontaneously. However, a small percentage of these tumors do not follow this course. Instead, they may develop into life-threatening hemangiomas by obstructing vital organs or may cause hemorrhage, anemia, infections, or Kasabach-Merritt syndrome, causing death of the child if left untreated (15). With the exception of IFN-α, there is at present no treatment for these complex juvenile hemangiomas (7, 8). Here we propose a novel in vivo model for exploring new strategies for the treatment of hemangiomas; i.p. infection of newborn rats with a high titer of the Marseille strain of mPyV results in the development of multiple cutaneous, peritoneal, and cerebral hemangiomas associated with severe hemorrhage and anemia, causing death of the animals within 3 weeks p.i. We provide evidence that cidofovir is highly effective in this hemangioma model. After inoculation of the rats with

Table 1  Effect of cidofovir on tumor incidence and severity in mPyV-infected (10⁶⁷ pfu) newborn rats

<table>
<thead>
<tr>
<th>Start of treatment (days p.i.)</th>
<th>Dose (mg/kg)</th>
<th>Number with cerebral hemangiomas</th>
<th>Mean lesion score</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25&lt;sup&gt;g&lt;/sup&gt;</td>
<td>6/10 (60%)</td>
<td>1.5 ± 1.7</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>3</td>
<td>25&lt;sup&gt;g&lt;/sup&gt;</td>
<td>4/6 (67%)</td>
<td>1.5 ± 1.7</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>6</td>
<td>25&lt;sup&gt;g&lt;/sup&gt;</td>
<td>6/10 (60%)</td>
<td>1.5 ± 1.7</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
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</table>

<sup>a</sup> Statistical significance was evaluated by the χ² test with Yates’ correction. Treatment was continued until 4 weeks p.i., at which time all animals were killed.

<sup>b</sup> Mean lesion standard or cerebral hemangioma development was estimated by the following standard: 4, large hemangiomas accompanied by multiple hemangiomas of moderate and small size; 3, large hemangioma and multiple smaller hemangiomas; 2, several small hemangiomas or one hemangioma of moderate size; and 1, a single, small hemangioma or hemangiomas only detectable by means of histological examination.

<sup>c</sup> Statistical significance was evaluated by the two-tailed, unpaired Student’s t test.

<sup>d</sup> Cidofovir was administered once a week, starting at the indicated time after infection.

<sup>e</sup> Cidofovir was administered five times a week.
a high virus load, s.c. cidofovir treatment started at 3 days p.i. resulted in complete protection against hemangioma development. When the start of treatment was delayed until cerebral hemangiomas were already macroscopically detectable (as evaluated by dissection of a parallel control group of rats), still a marked effect on survival and severity of the lesions was observed.

Although cidofovir has also been shown to inhibit the in vitro replication of many viruses, including mPyV (16), it is unlikely that this anti-polyomavirus activity accounts for the potent inhibitory effect of the compound on tumor growth, as seen in the present model. Earlier studies (17), based on titration of homogenized organs, have shown that no (detectable) replicative virus is produced in different organs of rats infected with mPyV. To confirm this, in the present study we performed (a) a titration of tissue homogenates for infectious virus content, (b) a dot blot DNA-DNA hybridization assay, and (c) a semiquantitative PCR for VP1 (i.e., a marker for replicating virus) on rat organs collected at different times p.i. Our results indicate that no viral replication takes place in these rat organs after infection with mPyV, because no viral DNA could be detected by means of titration or dot blot assay, and the amount of VP1 DNA in these organs (as assessed by PCR) gradually declined with time after infection and was, except for a weak signal in spleen, lungs (cidofovir-treated animals), and brain (control animals), no longer detectable at 18 days p.i.

Polyoma virus induces a variety of tumors in rodents and is capable of transforming cell cultures in vitro (18, 19). Three early viral proteins are assumed to be responsible for this behavior: small, middle, and large T (tumor) antigen (20), middle T carrying the cell-transforming activity. Middle T is predominantly associated with the plasma membrane (21) and binds and modulates the activity of several molecules involved in signal transduction, such as the Src family of tyrosine kinases, namely Src (22), Fyn (23), and Yes (24, 25), SHC (26), and the p85 regulatory subunit of phosphatidylinositol 3-kinase (27), resulting in constitutively activated tyrosine kinase receptors. From studies with several transgenic and chimeric mouse model systems (28, 29), it is evident that part of the tumorigenic potential of polyomavirus resides in the viral early region, and that polyomavirus middle T antigen-mediated tumorigenesis does not need viral replication or the whole viral life cycle. The rapid kinetics by which endothelial cells are transformed by the polyomavirus middle T antigen (18, 28) may account for the fact that only endothelial tumors (i.e., hemangiomas) are observed upon infection with the high virus titer used in this study.

Fig. 5. Histological section of a cerebral hemangioma showing endothelial cells (open arrows) surrounding a hemorrhagic area filled with blood and infiltration of hemosiderin-containing macrophages (closed arrow). Magnification, ×75.

Fig. 6. PCR analysis of VP1 DNA in spleen (s), kidney (k), liver (l), lungs (lu), and brain (b) obtained at different times after infection of 4-day-old rats with $10^6$ PFU of mPyV. Cidofovir treatment (25 mg/kg, once a week) was initiated at 3 days p.i.
Moreover, cidofovir was found to cause protection against hemangiomas when treatment was initiated at a time when brain tumors were already macroscopically visible. This activity may be attributable to a direct antitumor action of the compound (i.e., through apoptosis) or to an antiangiogenic effect of cidofovir. Recently, it has been shown that cidofovir elicits antitumoral activity by inducing apoptosis in both HPV-carrying and HPV-negative tumor cell lines but not in control cells (30). Also, intratumoral treatment with cidofovir resulted in the regression of established NPCs grafted to nude mice, and systemic treatment with cidofovir led to an arrest of NPC growth. Apoptosis appeared to be responsible for this effect (12).

At present, the stimulus for endothelial cell proliferation leading to hemangioma development in children is not known. There is no evidence that transformation of endothelial cells is taking place in juvenile hemangiomas, because spontaneous involution occurs in 90% of the cases. Nonetheless, our rat model does serve as a good functional model of hemangiomas for the following reasons: (a) the tumors are of the endothelial cell type; (b) there is involvement of vital organs (i.e., brain); (c) rats develop many of the side effects observed in hemangioma-bearing infants (i.e., hemorrhages, severe anemia, and splenomegaly); and (d) akin to the situation in humans, there is macrophage infiltration in the hemangiomas. In addition, because newborn animals are used, only compounds with sufficient selectivity (i.e., good activity and low toxicity) will lead to protection. Therefore, the model presented here may be useful for the in vivo identification of novel inhibitors of vascular tumor growth.

In this study, we have shown that clinically achievable doses of cidofovir (13) potently inhibit the growth of cutaneous and cerebral hemangiomas in newborn rats. This potent antitumor effect was accompanied by only a minor delay in the growth of the rats. Therefore, cidofovir deserves further consideration as a therapeutic agent for the treatment of hemangiomas.

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