The effect of low-dose cidofovir on the long-term outcome of polyomavirus-associated nephropathy in renal transplant recipients

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Abstract

Background. Polyomavirus-associated nephropathy (PVAN) has an unfavourable impact on graft survival. The cornerstone of therapy is early reduction of immunosuppressive medications; however, the rate of graft failure is still high. Antiviral drugs, such as cidofovir, are thought to have therapeutic effects, but the benefits of cidofovir in retarding the deterioration of PVAN are still a controversial issue.

Methods. Fourteen renal kidney recipients were diagnosed to have biopsy-proven PVAN between 2001 and 2006 in Chung-Shan Medical University Center with nearly 600 renal transplant recipients. After the diagnosis of PVAN, all patients were treated with a reduction of their original immunosuppressive medications with/without converting tacrolimus to cyclosporine. Eight of the 14 patients agreed to receive low-dose cidofovir (0.5 mg/kg) every 2 weeks for a total of six doses.

Results. During 30 ± 18 months of follow-up, three (37%) patients in the cidofovir-treated and three (50%) patients in the non-cidofovir-treated group experienced graft loss (P = 0.64). The rejection rate before PVAN diagnosis or other baseline characteristics of the patients between two groups were not significantly different. The long-term survival rate to graft loss and major graft functional decline with Kaplan–Meier analysis between the two groups were not significantly different (P = 0.898 and P = 0.243). In all demographic and clinical characteristics, we found that there was a tendency towards long-term major graft functional decline in the patients with acute rejection prior to PVAN diagnosis (P = 0.04).

Conclusions. We concluded that (1) there was no obvious effect of low-dose cidofovir on long-term graft survival in patients with PVAN, and (2) acute rejection prior to PVAN diagnosis was a potential risk factor for poorer long-term graft outcome.

Keywords: acute rejection; cidofovir; graft outcome; polyomavirus-associated nephropathy; renal transplantation

Introduction

Polyomavirus (BK type)-associated nephropathy (PVAN) has increasingly been noted as a significant cause of graft dysfunction or failure [1–2]. The prevalence of PVAN is estimated to be 1–10% and has shown a stepwise increase in the past decade [3–5]. Despite decreasing immunosuppressive medications being the cornerstone of treatment, the protocols and responsive rates are heterogeneous, with a renal graft loss of between <10% and 100% [6–7]. In patients with progressive graft dysfunction who do not respond to a reduction of immunosuppressants, antiviral agents such as cidofovir or leflunomide and intravenous immunoglobulin have been used with anecdotal success [8–10]. Recently, some reports confirmed that adjuvant cidofovir treatment resulted in an improved clinical course and a blood viral load reduction in most patients [11–12]; however, not every report has confirmed this [13].

We followed up 14 renal kidney recipients with biopsy-proven PVAN for a mean of 30 ± 18 months to determine the effect of low-dose cidofovir on long-term graft survival compared with a reduction of immunosuppressants alone.

Materials and methods

Patients

Between January 2001 and June 2006 in Chung-Shan Medical University, 14 patients were diagnosed to have PVAN. This diagnosis in all patients was confirmed by a fine-needle biopsy, which was performed when unexplained graft dysfunction was noted. PVAN was defined by the typical viral cytopathic changes in the epithelium of tubules, glomeruli and collecting ducts and further confirmed by positive immunohistochemical nuclear staining...
Follow-up post-PV AN diagnosis (months) 32.25 ± 16.25

Follow-up of PV AN

Management of PV AN—immunosuppression reduction and cidofovir therapy

The maintenance immunosuppressive medications were reduced immediately after the diagnosis of PVAN. The blood concentration of calcineurin inhibitor (tacrolimus or cyclosporine) and sirolimus was reduced to one-third to a half of the original level. In most patients, tacrolimus was converted to low-dose cyclosporine. The dose of mycophenolate mofetil (MMF) was reduced by half in all patients. Low-dose corticosteroid therapy (prednisolone 5 mg QD) was continued if it was already being used.

Eight out of 14 patients agreed to participate in low-dose cidofovir therapy after signing informed consent. The regimen of cidofovir was 0.5 mg/kg every 2 weeks for a total of six doses. Drug-associated adverse effects such as systemic effects (fever, nausea and skin rash), renal toxicity and bone marrow toxicity were closely monitored. No patients had to be withdrawn from this treatment because of significant adverse effects.

Follow-up of PVAN

We followed up the patients for a mean period of 30 ± 18 months. Serum creatinine levels were checked at least monthly. After a qualitative urine and blood BK virus PCR was available in our centre in 2006, it was performed on every patient at least every 6 months. A follow-up biopsy was performed if unexplained deterioration of renal graft function was noted. Graft loss was defined by a patient needing to return to dialysis or re-transplant. Major graft functional decline was defined by a graft loss or doubling of serum creatinine at PVAN diagnosis.

Statistical analyses

Statistical analyses used SPSS software for Windows (version 10.0; SPSS, Chicago, IL, USA). The t-test, Mann-Whitney U-test or Fisher’s exact test was used depending on the nature of the variables. The Kaplan–Meier analysis was used to estimate the probability of graft survival using the diagnosis date as the starting date of the survival curve. Differences between survival curves were tested with a log-rank test. A P-value of <0.05 was considered as statistically significant.

Results

The average age of the 14 patients at PVAN diagnosis was 52 ± 15 years; 10 were male and 4 were female. All patients had received deceased kidney transplantation and induction therapy with an anti-IL2 antibody. Three (21%) patients received cyclosporine-based, eight (57%) tacrolimus-based and three (21%) tacrolimus + sirolimus-based immunosuppressive regimens. The serum creatinine levels in nadir and at the time of PVAN diagnosis were 1.36 ± 0.33 and 2.50 ± 0.87 mg/dl, respectively. The median time between transplantation and PVAN diagnosis was 12.8 months (range, 7.3–29.6). A comparison of the patient characteristics between the cidofovir-treated group and non-cidofovir-treated group is shown in Table 1. There were closely comparable demographic information and baseline characteristics. A summary of therapeutic interventions and graft outcomes after the median follow-up of 30 ± 18 months is shown in Table 2. Kaplan–Meier estimates at the rate of graft loss and major graft functional decline between the cidofovir-treated and non-cidofovir-treated group are shown in Figure 1A and B. As shown, the long-term outcome of graft function (graft loss or major graft function decline) between these two groups was not significantly different (P = 0.898 and
A

B

Fig. 1. Graft outcome of PVAN in renal transplant recipients treated with and without cidofovir since diagnosis. The Kaplan–Meier survival rate was plotted to show the rate of occurrence of (A) graft loss (defined by a patient needing to return to dialysis or re-transplant) and (B) major graft functional decline (defined by graft loss or doubling of serum creatinine at PVAN diagnosis). P-value by the log-rank test between the two groups is shown.

Two patients (25%) in the cidofovir-treated and two (33%) in the non-cidofovir-treated group received follow-up graft biopsies due to an unexplained deterioration of graft function. All histologies demonstrated a decreasing staining of BK virus but a progression of tubulointerstitial damage compared with the previous results, and one patient in the cidofovir-treated group had concurrent acute rejection. Qualitative blood BK virus PCR performed on the eight patients with functioning graft function after treatment for PVAN revealed all negative results. There were no significant adverse effects in patients treated with this dose of cidofovir. In univariate analysis, we found that there was a tendency towards long-term major graft functional decline in the patients with acute rejection prior to PVAN diagnosis (P = 0.04) (Table 3).

Discussion

The potential graft loss rate for PVAN in the previously published literature varies widely, from <10 to >90% [7]. This is probably due to heterogeneous patient characteristics, therapeutic interventions and the duration of follow-up. Nevertheless, the mean of the graft loss rate was still high. In our study, six patients (43%) had graft loss during an average of 30 months of follow-up and ~67% had graft loss at 5 years with the Kaplan–Meier analysis. Contrary to our results and other reports, Wadei et al. reported <20% graft loss at 3 years [14]. The author referred the results to early accurate diagnosis and a reduction of immunosuppressants because a high proportion were diagnosed on surveillance biopsies. However, we think that a shorter duration of follow-up than ours could also explain this.

Many studies have confirmed the role of reducing immunosuppressants in the stabilization of renal function [6,15,16]. However, this increases the risk of acute rejection and not all patients respond to this therapy [13]. Antiviral agents such as cidofovir or leflunomide and intravenous immunoglobulin are increasingly being studied as an adjuvant treatment for the reduction of immunosuppressants. Cidofovir, a cytosine–phosphate analogue, has in vitro activity against various polyomavirus strains [17,18]. Low-dose cidofovir has been studied in the treatment of PVAN in renal transplant recipients but the efficacy has not been definitely confirmed as yet [19,20]. Recently, Kuypers et al. found that no allograft loss occurred in the cidofovir-treated recipients, which was contrary to 9 of 13 managed by the reduction of immunosuppressants alone during 4–40 months

In Table 2, the therapeutic interventions and graft outcome in 14 patients with PVAN are summarized.

Table 2. Therapeutic interventions and graft outcome in 14 patients with PVAN

<table>
<thead>
<tr>
<th>Immunosuppressive adjustment</th>
<th>Cidofovir treated (n = 8)</th>
<th>Non-cidofovir treated (n = 6)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine conversion, n (%)</td>
<td>5 (63)</td>
<td>4 (67)</td>
<td>0.6870</td>
</tr>
<tr>
<td>Reduced baseline immunosuppression, n (%)</td>
<td>8 (100)</td>
<td>6 (100)</td>
<td></td>
</tr>
<tr>
<td>Acute rejection after PVAN diagnosis, n (%)</td>
<td>1 (12)</td>
<td>0 (0)</td>
<td>0.3688</td>
</tr>
<tr>
<td>Histological progression in patientsa with a follow-up biopsy, n (%)</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>–</td>
</tr>
<tr>
<td>Graft loss, n (%)</td>
<td>3 (37)</td>
<td>3 (50)</td>
<td>0.6400</td>
</tr>
</tbody>
</table>

aDefined by a progression of interstitial fibrosis and/or tubular atrophy in the follow-up biopsy.
Cidofovir on polyomavirus-associated nephropathy

Table 3. The variables compared between group with (group A) and without (group B) major graft functional decline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 8)</th>
<th>Group B (n = 6)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.58 ± 12.51</td>
<td>53.24 ± 13.39</td>
<td>0.8484</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>5/3</td>
<td>5/1</td>
<td>0.3932</td>
</tr>
<tr>
<td>HLA-AB mismatch 0, 1, 2, 3 (n)</td>
<td>0/1/6/1</td>
<td>0/0/4/2</td>
<td>0.4776</td>
</tr>
<tr>
<td>HLA-DR mismatch 0, 1, 2 (n)</td>
<td>0/5/3</td>
<td>1/4/1</td>
<td>0.3939</td>
</tr>
<tr>
<td>PRA &gt;20%, n (%)</td>
<td>0 (100)</td>
<td>0 (100)</td>
<td>–</td>
</tr>
<tr>
<td>Nadir serum creatinine level (mg/dl)</td>
<td>1.35 ± 0.38</td>
<td>1.38 ± 0.29</td>
<td>0.8600</td>
</tr>
<tr>
<td>Time between transplantation and PVAN diagnosis (months)</td>
<td>14.93 ± 7.40</td>
<td>13.08 ± 4.16</td>
<td>0.5938</td>
</tr>
<tr>
<td>Immunosuppressive regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine based, n (%)</td>
<td>1 (13)</td>
<td>2 (25)</td>
<td>0.6378</td>
</tr>
<tr>
<td>Tacrolimus based, n (%)</td>
<td>5 (63)</td>
<td>3 (50)</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus-t-sirolimus based, n (%)</td>
<td>2 (25)</td>
<td>1 (17)</td>
<td></td>
</tr>
<tr>
<td>Induction therapya, n (%)</td>
<td>8 (100)</td>
<td>6 (100)</td>
<td></td>
</tr>
<tr>
<td>Delayed graft function, n (%)</td>
<td>1 (13)</td>
<td>0 (0)</td>
<td>0.3688</td>
</tr>
<tr>
<td>Acute rejection prior to PVAN diagnosis, n (%)</td>
<td>4 (50)</td>
<td>0 (0)</td>
<td>0.0400</td>
</tr>
<tr>
<td>Acute rejection after PVAN diagnosis, n (%)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>0.3688</td>
</tr>
<tr>
<td>Serum creatinine level at the time of PVAN diagnosis (mg/dl)</td>
<td>2.81 ± 1.05</td>
<td>2.08 ± 0.26</td>
<td>0.0951</td>
</tr>
<tr>
<td>Histological type of PVANb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A, n (%)</td>
<td>2 (25)</td>
<td>2 (25)</td>
<td>0.7327</td>
</tr>
<tr>
<td>Type B, n (%)</td>
<td>6 (75)</td>
<td>4 (67)</td>
<td></td>
</tr>
<tr>
<td>Type C, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Follow-up post-PVAN diagnosis (months)</td>
<td>32.38 ± 21.19</td>
<td>39.17 ± 23.73</td>
<td>0.5828</td>
</tr>
</tbody>
</table>

aInduction therapy with Daclizumab (Zenapax®).
bHistological grading according to Drachenberg et al. [21].

of follow-up [11]. Nevertheless, a larger group of patients studied by Wadei et al. did not suggest that cidofovir had any additional beneficial effects on graft function [14]. In our study, the 1-, 2-, 3-, 4- and 5-year graft survival rates with the Kaplan–Meier estimate were 100, 88, 66, 33 and 33% in the cidofovir-treated group and 100, 83, 33, 33 and 33% in the non-cidofovir-treated group (P = 0.898). The survival rate to major graft functional decline was also statistically insignificant (P = 0.243). Therefore, we did not see extra benefits of cidofovir on long-term graft survival than the reduction of immunosuppressants alone. In addition, since the introduction of cidofovir in the treatment of PVAN, there is a paucity of data relating to the optimal dose and duration of cidofovir therapy. In consideration of its nephrotoxicity and pharmacokinetic characteristics, most authors agreed to prescribe low doses of cidofovir [11,14,19,20]. However, the doses in these studies were heterogeneous, ranging from 0.25 to 1.0 mg/kg weekly to every 2 weeks and the therapeutic duration also varied from a total of 4 doses to about 10 doses. Some authors guided the duration by blood BK viral load or graft biopsy [11,14]. Based on these prior reports, we chose the protocol of 0.5 mg/kg every 2 weeks for a total of six doses. We did not administer additional doses because all patients had negative blood BKV PCR during the follow-up. More studies are needed to clarify the optimal dose and duration of cidofovir therapy.

In all demographic and clinical characteristics, we found that there was a tendency towards long-term major graft functional decline in the patients with acute rejection prior to PVAN (P = 0.04). This was unlike previous studies, which showed that the degree of interstitial fibrosis and tubular atrophy was predictive [14,21]. Our findings might be explained by graft damage from acute rejection itself and/or further graft damage due to the occurrence of PVAN after rescue therapy for acute rejection. In addition, misdiagnosing PVAN to acute rejection or concurrence of both conditions in the biopsies performed prior to PVAN diagnosis could be other explanations. This reminds us that the PCR assay of BKV DNA can play a helpful role in distinction between them [22]. Unfortunately, we did not perform it in the four episodes of acute rejection prior to PVAN diagnosis due to the technique being unavailable at that time in our hospital.

Although the blood BK virus PCR demonstrated negative results during the follow-up, it seemed that not all patients had stabilized renal function. This might imply that the reduction of immunosuppressants with/without cidofovir treatment indeed reduced the replication of BK virus, but its damage could continue.

Even though this study has to the best of our knowledge the longest duration of follow-up for the effect of cidofovir on graft survival, several biases may have existed. Firstly, this is a non-randomized control study and the patient number is limited. Secondly, although there are no significant differences of demographic and clinical manifestation between the two groups, the heterogeneity of baseline immunosuppressive medications and the mode of reducing maintenance immunosuppressive medications might actually influence the results. Thirdly, even though the follow-up biopsies in the four patients all revealed a decreasing staining of BK virus and a progression of tubulointerstitial damage, it is still arbitrary to say that the graft function decline was only due to PVAN in consideration of the limited numbers of biopsies.

In conclusion, we found that there was no obvious effect of low-dose cidofovir on long-term graft survival in patients with PVAN, and acute rejection prior to PVAN diagnosis was a potential risk factor for poorer long-term graft outcome.
Conflict of interest statement. None declared.

References


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