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Initial experience with oral valganciclovir for pre-emptive cytomegalovirus therapy after lung transplantation

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Erste Erfahrungen mit oralem Valganciclovir zur präemptiven Behandlung des Zytomegalievirus nach Lungentransplantation

Zusammenfassung. *Hintergund:* Opportunistische Virusinfekte nach Lungentransplantation sind am häufigsten auf Zytomegalieviren (CMV) zurückzuführen. Orales Valganciclovir ist eine Prodrug von Ganciclovir und wurde als potentielles Agens für Prophylaxe und Behandlung von CMV-Infektionen eingeführt. Wir präsentieren unsere initiale Erfahrung mit oralem Valganciclovir *zur präemptiven CMV-Therapie nach Lungentransplantation.*

Methode and Patienten: Wir fassen unsere Erfahrung mit präemptiver CMV-Therapie mit oralem Valganciclovir bei 19 Patienten nach Lungentransplantation mit positiver CMV – polymerase chain reaction (PCR) in Plasma oder bronchoalveolärer Lavage zusammen. Es wurde keine manifeste CMV-Erkrankung beobachtet. Therapeutische Valganciclovirdosis waren je nach Nierenfunktion und Leukozyten 450 bis 1800 mg täglich. Die Behandlung wurde bis zum Nachweis einer negativen CMV-PCR, jedoch mindestens 14 Tage durchgeführt.

Ergebnisse: 3 Patienten erhielten 2 Zyklen Valganciclovir, 16 Patienten einen Behandlungszyklus. 11 Patienten (57,9%) wurden aufgrund einer positiven CMV-PCR im Plasma behandelt, bei 8 Patienten (42,1%) war eine positive CMV-PCR nur in der bronchoskopisch gewonnenen Lavage nachweisbar. Therapiebeginn war 896 ± 1186 Tage nach der Transplantation (108–3911 Tage) mit mittleren CMV-PCR-Werten von 45536 ± 149294 Kopien (426–706000). Nach 22 ± 10 (7–50) Tagen fiel die CMV-PCR in allen Fällen unter die Nachweisgrenze (< 400 Kopien). Eine milde Leukopenie trat bei 7 Patienten (36,8%) auf. Sonstige potentiell therapiebedingte Nebenwirkungen wie Neutropenie, Anämie, gastrointestinale Probleme oder Verschlechterung der Nierenfunktion traten nicht auf.

Schlussfolgerungen: Präemptive CMV-Therapie mit oralem Valganciclovir nach Lungentransplantation scheint wirksam und sicher zu sein. Jedoch sind regelmäßige Kontrollen des Blutbildes notwendig, um eine sich entwickelnde Leukopenie rechtzeitig zu erkennen.

Summary. *Background:* The most common opportunistic viral pathogen after lung transplantation is cytomegalovirus (CMV). Oral valganciclovir, a prodrug of ganciclovir, has been introduced as a potential drug for prophylaxis and treatment of CMV infection and disease in lung transplantation. The goal of this study was to describe our initial experience with oral valganciclovir for pre-emptive treatment of CMV infections after lung transplantation.

Methods and patients: We summarize our experience with 19 patients who underwent lung transplantation and received pre-emptive oral valganciclovir therapy in the situation of positive CMV polymerase chain reaction (PCR) in either plasma or bronchoalveolar lavage. None of the patients presented with manifest CMV disease. Treatment dosage of valganciclovir was 450 mg to 1800 mg daily, depending on renal function and white blood count. Treatment was continued until the CMV PCR became negative, in any case for a period of at least 14 days.

Results: Three patients received two courses of pre-emptive oral valganciclovir; 16 patients were treated once. Eleven patients (57.9%) were treated because of a positive plasma CMV PCR; in eight patients (42.1%) the PCR was positive only in bronchoalveolar lavage. Therapy was initiated 896 ± 1186 days (range 108–3911) after transplantation with a mean CMV PCR of 45,536 ± 149,294 copies (range 426–706,000). In all cases the PCR fell below detectability (< 400 copies) after a period of 22 ± 10 days of treatment (range 7–50 days). Mild to moderate leucopenia was observed in seven patients (36.8%) during treatment. None of the patients developed new onset of other potentially drug-related disorders such as neutropenia, anemia, deterioration of renal function or gastrointestinal disorder.

Conclusions: Pre-emptive therapy with oral valganciclovir for CMV infections detected by PCR in either plasma or bronchoalveolar lavage after lung transplantation seems to be efficacious and safe. However, regular blood counts should be performed to detect developing leucopenia.

Key words: Lung transplantation, cytomegalovirus, CMV, pre-emptive therapy, valganciclovir.

Background

The most common opportunistic viral pathogen after lung transplantation is cytomegalovirus (CMV); thus, regular screening has been adopted almost uniformly in follow-up protocols. The most widespread screening methods are detection of pp65 antigen and quantitative polymerase chain reaction (PCR). Pre-emptive therapy with oral or intravenous ganciclovir is widely used if screening examinations show increased levels of CMV in either blood or bronchoalveolar lavage (BAL), and the incidence of manifest CMV disease has been considerably reduced with this therapeutic approach.

Oral valganciclovir is an L-valyl ester prodrug of ganciclovir with a bioavailability comparable to that of intravenous ganciclovir, which was initially mainly used for treatment of CMV retinitis in HIV-positive patients. Application of valganciclovir in transplantation of solid organs – especially for prophylaxis – has been described in patients undergoing liver, kidney, heart and pancreas transplantation [1–3] but there are very limited data on its application after lung transplantation. However, patients receiving lung transplants are a collective with substantial differences regarding CMV screening and treatment requirements, compared with recipients of other solid organs. Since relatively high levels of immunosuppression are required in lung transplantation, these patients are especially prone to CMV infections. Many centers include routine surveillance bronchoscopies in their follow-up protocols, and these provide a very sensitive screening method for CMV infections. This paper describes our initial experience with pre-emptive oral valganciclovir therapy in patients after lung transplantation, with a focus on organ-specific requirements.

Methods and patients

All 19 patients who underwent lung transplantation in our institution and who received pre-emptive oral valganciclovir therapy because of positive quantitative CMV PCR in either plasma or BAL entered the study. Thirteen patients (68.4%) were male; six female (31.6%). Mean age was 46.4 ± 12.8 years. Underlying diagnoses for lung transplantation were: chronic obstructive pulmonary disease (8 patients, 42.1%), pulmonary fibrosis (4 patients, 21.1%), primary pulmonary hypertension (2 patients, 10.5%), cystic fibrosis (4 patients, 21.1%) and chronic thromboembolic pulmonary hypertension (1 patient, 5.2%). A triple-drug immunosuppression consisting of either cyclosporine A or tacrolimus, plus mycophenolat mofetil and corticosteroids was standard baseline therapy. One patient with impaired kidney function received rapamycin in addition, and one patient received azathioprine instead of mycophenolat mofetil.

For all patients, irrespective of the CMV status of donor and recipient, routine perioperative CMV prophylaxis consisted of either intravenous ganciclovir 2 x 5 mg/kg per day or oral valganciclovir 2 x 900 mg per day for the first three weeks after transplantation, followed by either oral ganciclovir 3 x 1000 mg or valganciclovir 2 x 450 mg for an additional 10 weeks. Four intravenous doses of 100 mg human anti-CMV hyperimmune globulin were given concomitantly at 7, 14, 21 and 28 days after transplantation.

Plasma PCR was routinely used for weekly CMV screening during the first two months after transplantation, and thereafter at every patient visit to the outpatient department, which was at least monthly in the first year after transplantation and then bimonthly. Additional testing was performed according to clinical necessity. Surveillance bronchoscopies were performed at weeks 1 and 2 and months 1, 2, 3, 6 and 12 after transplantation, together with a semi-quantitative BAL PCR, as part of the routine screening for infection and rejection.

If PCR detected more than 400 CMV copies in plasma and/or more than 1000 CMV copies in BAL, pre-emptive therapy was initiated. Standard treatment dosage was valganciclovir 2 x 900 mg daily; however, depending on renal function and white blood count the daily dosage was reduced to 450 mg per day in some patients. Treatment was continued until the CMV PCR became negative, in any case for a period of at least 14 days. During treatment, check-ups were usually performed weekly in patients with mild elevation of CMV levels and no other noticeable problems after 14 days. Further check-ups were performed depending on clinical necessity, in any case at least bimonthly.

Results

Three patients received two courses of pre-emptive oral valganciclovir; 16 patients were treated once. Eleven patients (57.9%) were treated because of a positive plasma PCR; in eight patients (42.1%) the PCR was positive only in BAL. None of the patients presented with symptoms of manifest CMV disease. Ten recipients tested positive for CMV IgG: three of them received organs retrieved from donors negative for CMV IgG, six received organs from donors positive for CMV IgG and in one case the CMV status of the donor was unknown. Nine recipients tested negative for CMV IgG and all received organs from donors testing positive. No significant differences were observed between IgG-positive and IgG-negative recipients.

Increased numbers of CMV copies were demonstrated (mean PCR 45,536 ± 149,294 copies, range 426–706,000) and pre-emptive therapy initiated on average 896 ± 1186 days (range 108–3911) after transplantation. Peak PCR levels in BAL were higher than those in plasma, although median levels were comparable. In all cases of positive plasma PCR, BAL PCR was also positive if it was performed concomitantly; however, in eight cases a positive BAL PCR did not coincide with a positive plasma PCR. Simultaneous reduction greater than 10% in forced expiratory volume in 1 second as percent predicted (FEV1%) was observed in four patients.

Three patients showed signs of acute rejection in the transbronchial biopsy and were treated with a methylprednisolone bolus therapy of 3 x 1000 mg, together with concomitant oral antibiotic and inhalative antimycotic prophylaxis. Interestingly, only one patient presenting with acute rejection in histology also had a decrease in lung function values, whereas the other two patients had stable function. After treatment, lung function recovered to initial values in all cases.

The CMV PCR fell below the detection limit (< 400 copies) in all cases after a period of 22 ± 10 days of treatment (range 7–50). The required treatment period in patients with positive BAL PCR was slightly shorter than in patients with positive plasma PCR (19 ± 3 days vs.

Table 1. Patient data

Pat.	Age	TX	Indication	D	R	PCR	Copies	d	Crea.	WBC	Dose	Hb	FEV1%	Rej.
1	49	SLTX	Fibrosis	?	+	Plasma	76400	13	1.21	5.1	2x900	13.0	stable	
2	29	BLTX	PPH	+	–	BAL	3300	21	2.20	6.3	2x900	13.3	stable	
3	30	BLTX	CF	–	+	BAL	7110	21	1.21	10.6	2x900	17.0	stable	
4	28	BLTX	PPH	+	-	Plasma	85100	50	4.89	3.7	1x450	10.5	stable	
5	50	BLTX	CTEPH	+	–	BAL	932	21	1.48	5.1	2x450	12.0	81→64	
6	56	BLTX	COPD	–	+	BAL	31400	21	1.08	7.7	2x450	12.5	stable	A2B1–2
7	42	SLTX	Fibrosis	+	–	Plasma	4520	33	1.47	1.8	2x900	11.1	stable	
8	27	BLTX	CF	–	+	Plasma	3810	37	1.46	2.9	2x450	11.2	stable	
9	58	BLTX	COPD	+	–	BAL	3810	14	1.55	4.9	2x450	10.7	stable	
10	47	BLTX	COPD	+	+	BAL	1820	20	3.70	8.6	2x450	9.9	73→66	
11	62	BLTX	COPD	+	+	BAL	706000	14	0.79	7.6	2x900	11.4	75→66	A1 B1
12	57	BLTX	COPD	+	-	Plasma	26700	22	1.23	1.9	2x900	10.2	stable	
13	45	BLTX	COPD	+	+	Plasma	1128	10	0.85	6.9	2x900	13.5	74→36	
14	57	BLTX	Fibrosis	+	+	BAL	7230	20	2.0	4.2	2x450	11.6	stable	
15	58	BLTX	COPD	+	–	Plasma	7100	10	1.81	7.0	2x450	8.8	stable	
16	35	BLTX	CF	+	–	Plasma	426	20	1.09	4.8	2x900	12.1	stable	
17	31	BLTX	CF	+	–	Plasma	4080	21	1.23	2.0	2x450	11.9	stable	
18	56	BLTX	COPD	+	+	Plasma	3680	21	0.87	5.6	2x900	10.7	stable	A1–2B1
19	63	BLTX	Fibrosis	+	+	Plasma	6810	7	1.22	1.1	1x450	10.9	stable	

Pat. Patient number; *TX* Transplantation; *SLTX* Single lung transplantation; *BLTX* Bilateral lung transplantation. *Indication*: *CF* Cystic fibrosis; *COPD* Chronic obstructive pulmonary disease; *CTEPH* Chronic thromboembolic pulmonary hypertension. *PPH* Primary pulmonary hypertension. *D* Donor CMV-IgG status. *R* Recipient CMV-IgG status. *PCR* Diagnosis of CMV infection by polymerase chain reaction. *Copies* Highest number of CMV copies found in PCR. *d* Days until CMV PCR showed negative result. *Crea*. Highest serum creatinine (mg/dl) during treatment. *WBC* Lowest white blood count during treatment. *Dose* Treatment dose (mg). *Hb* Lowest blood hemoglobin level (mg/dl) during treatment. *FEV1%* Deterioration simultaneous with CMV infection (forced expiratory volume in 1 second as percent predicted). *Rej*. Rejection in transbronchial biopsy according to ISHLT grading.

22 ± 13 days); however, this was not statistically significant.

Mild to moderate leucopenia was observed in seven patients (36.8%) during treatment. After discontinuation of treatment, white blood counts recovered to normal levels at the next screening in five patients. In one patient, prolonged clinically asymptomatic leucopenia with white blood counts between 2000 and 2500/µl was observed for eight months. During this period the CMV PCR and repeated screening for viral infections was negative at all times. Valganciclovir certainly could have been a trigger for this prolonged leucopenia; however, ultimately the causative factors remain unclear. One other patient showed borderline leucopenia after the time of transplantation; that is, before the initiation of valganciclovir treatment. This patient presented with recurrent CMV infections and was treated twice with pre-emptive valganciclovir. Dosage was reduced to 450 mg per day because of the pre-existing leucopenia. During this period the average leukocyte count of 3000/µl dropped to 1100/µl; however, after discontinuation of the drug, the count increased to initial values.

None of the patients had new onset of other potentially drug-related disorders such as neutropenia, anemia, deterioration of renal function or gastrointestinal disorder.

After a follow-up period of at least three months after pre-emptive therapy with valganciclovir, three patients suffered recurrent CMV infections and had to receive a second course of pre-emptive valganciclovir for a mean duration of 29 days (range 21–43). CMV PCR levels were between 2740 and 10,300 copies in those cases. Sixteen patients did not have any recurrent CMV infections. No development of drug resistance was observed clinically.

No patient presented with elevated CMV copies in plasma or BAL PCR while receiving prophylactic medication with either ganciclovir or valganciclovir and CMV hyperimmune globulin. All patient data are given in Table 1.

Discussion

CMV remains the single most important opportunistic pathogen following transplantation of solid organs [4]. Thus, the adequate prevention, detection and treatment of CMV infection and disease are of utmost importance in order to avoid acute or long-term impairment of the allograft function. Recipients of lung transplants are especially at risk, since the lungs are a major site of CMV latency and recurrence [5].

Potential mechanisms of CMV infection are: transmission by the donor organ, transmission by blood products, or reactivation of latent virus in the recipient. Although CMV prophylaxis is almost uniformly administered in the initial post-transplant period, the ideal strategy for prevention remains controversial, primarily because of the lack of randomized controlled trials comparing regimens [6]. Some studies suggest that, in particular, infec-

tions soon after transplant increase the incidence of bronchiolitis obliterans syndrome (BOS) [7], but others have not detected a decreased risk for BOS in the absence of CMV [8].

Various methods are used to detect CMV infection. Screening methods include testing for pp65 antigenemia, PCR assays, hybrid capture assays and shell viral assay. CMV disease is characterized by tissue invasion in histology or a by clinical syndrome which, after exclusion of other etiologies, potentially includes anorexia, malaise, fever, leucopenia, thrombocytopenia, and respiratory and hepatic involvement.

After detection of CMV antigenemia, pre-emptive therapy is a potential approach for reduction of the incidence of CMV disease [9] and has been described as efficacious and cost-effective [10]. Such an approach can be used instead of CMV prophylaxis in the early post-transplant period or in the follow-up of patients after an initial period of routine CMV prophylaxis, as in our center.

Ganciclovir is probably the most widely used drug for prophylaxis and treatment of CMV after transplantation of solid organs [11] and can be administered orally or intravenously. However, a ganciclovir-resistant CMV disease rate of 6% was recently described in recipients of lung transplants [12]. Valganciclovir has been developed as a treatment for CMV in immunocompromised patients. It was initially mainly used as a treatment of CMV retinitis in HIV-positive patients and in patients after bone marrow transplantation [13] but was soon also frequently used in patients after transplantation of solid organs. Valganciclovir has a 10-fold greater bioavailability than oral ganciclovir and might be used as a prophylaxis as well as for treatment of CMV [14]. It might replace intravenous ganciclovir, providing a potentially more cost-effective, safer and more convenient option for the management of CMV [15].

Potential side effects of valganciclovir include leucopenia, neutropenia, anemia, deterioration of renal function and gastrointestinal disorder. These are similar to those of ganciclovir. In our experience, the most common side effect is transitional leucopenia, thus warranting regular screening during therapy. One of our patients showed prolonged, clinically asymptomatic leucopenia after treatment with valganciclovir, without any other signs of myelosuppression. Repeated screening for viral infections during this period showed invariably negative results; however, a link between this prolonged leucopenia and the use of valganciclovir cannot be excluded. No other drug-related side effects occurred in our patient collective.

Dose adjustment is required in cases of renal impairment, because of reduced clearance [16]. However, in our patient collective no deterioration in renal function was observed in any patient, and no further deterioration in those with pre-existing impairment in renal clearance. In most cases the dose was reduced to 2×450 mg per day, and in one patient with severe renal impairment to only 450 mg per day.

We found that dose adjustment has to be considered on an individual basis, taking into account mainly the severity of CMV infection, the renal function and white blood count.

Valganciclovir is currently more expensive than intravenous ganciclovir given in standard dosage. However, since hospitalization can be avoided with oral treatment, the overall costs for a pre-emptive treatment cycle might even be less than with ganciclovir.

Lower resistance rates with valganciclovir than with oral ganciclovir have been described [17]. Clinically, we did not observe any resistance to treatment with valganciclovir. Three patients required a second treatment cycle; however, all of them had an interval of at least three months between the cycles and had repeatedly negative CMV PCR results during the interval.

We conclude that valganciclovir is an efficacious and safe drug for pre-emptive CMV therapy after lung transplantation; however, during its use regular blood counts should be performed to detect any developing leucopenia. With an acceptable profile of side effects, valganciclovir provides a bioavailability comparable to that of intravenous ganciclovir, together with the advantages of oral application.

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