

A Successful Treatment Story Using High Dose of Intravenous Ganciclovir in Resistant Cytomegalovirus Hepatitis in Kidney Transplanted Patient: Case Report and Literature Review

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Abstract

Cytomegalovirus is a double stranded DNA virus which causes a wide spectrum of infection. Ganciclovir is considered the drug of choice in treating Cytomegalovirus infection. However, resistance to ganciclovir makes the management difficult especially in kidney transplanted patients where the other treatment options carry a high risk of nephrotoxicity. High dose ganciclovir maybe an alternative that can achieve cure despite resistance giving a chance to avoid nephrotoxic medication.

Keywords: Cytomegalovirus; Hepatitis; Kidney transplant; Ganciclovir resistance

Case Report

This is a 15-year-old, Qatari male, who is a known case of end stage renal disease secondary to posterior urethral valve and reflux nephropathy. He underwent uneventful kidney transplant from live, none related donor. Post-transplant, he was kept on mycophenolate 750 mg twice daily, tacrolimus 5mg twice daily and prednisolone 5mg as immunosuppressive therapy. His antimicrobial prophylaxis regimen contained Co trimoxazole 960 mg 3 times per week and valganciclovir 450 mg daily. His pre-transplant work up showed negative Cytomegalovirus (CMV) serology.

Ninety days post-transplant, he presented to the hospital complaining of progressive epigastric pain without any other associated abdominal symptoms. On examination, the patient was stable vitally and afebrile. His weight was 46 Kg and height 151 cm. His abdominal examination was not remarkable for organomegaly or tenderness. Patient's laboratory investigation showed, WBC $3.4 \times 10^3/\mu\text{L}$, absolute neutrophils count $2.3 \times 10^3/\mu\text{L}$, Hb 12.7 mg/dL, platelets $136 \times 10^3/\mu\text{L}$, Creatinine 76 $\mu\text{mol/L}$, ALT 602 U/L, AST 255 U/L, Total bilirubin 4.9 $\mu\text{mol/L}$, Alkaline phosphatase 371 Unit/L and Cytomegalovirus PCR 170,842 IU/mL. Liver biopsy was done see **Figures 1 and 2**.

The patient was diagnosed as a case of cytomegalovirus hepatitis. So, he was started on intravenous ganciclovir 5 mg/Kg twice daily. After one week follow up, his laboratory results were still showing persistent elevation of the liver enzymes (ALT 636 U/L, ASL 238 U/L) and Cytomegalovirus PCR (177,089 IU/mL). Resistant CMV was suspected. The genotyping result of Cytomegalovirus showed CMV UL97 mutation: M460V, C603W. In consideration of avoiding nephrotoxic medication (Foscarnet and Cidofovir), a high dose of Intravenous ganciclovir (10 mg Kg twice daily) was started. Day five post high dose ganciclovir, CMV PCR count was showing marked reduction (39,475 IU/mL) and liver enzymes started to improve. High dose Intravenous ganciclovir was continued for 2 weeks. Then it was shifted to oral valganciclovir 900 mg twice daily to facilitate home discharge. Before discharge, patient's laboratory results were showing CMV PCR 10,077 IU/mL, ALT 179 U/L, AST 98 U/L, wbc $3.7 \times 10^3/\mu\text{L}$, absolute neutrophils count $2.3 \times 10^3/\mu\text{L}$, Hb12.3 mg/dL, platelet $195 \times 10^3/\mu\text{L}$, Creatinine 79 $\mu\text{mol/L}$.

Two weeks later, outpatient follow up showed WBC $0.7 \times 10^3/\mu\text{L}$, absolute neutrophils count $0.4 \times 10^3/\mu\text{L}$, lymphocytes $0.2 \times 10^3/\mu\text{L}$, Platelet $201 \times 10^3/\mu\text{L}$, Hb 10.3 mg/dL, ALT 25 U/L, AST 25 U/L, creatinine 85 $\mu\text{mol/L}$, CMV PCR 197 IU/mL. Peripheral smear showed Leukopenia with marked neutropenia and lymphocytopenia. Valganciclovir was stopped and high dose ganciclovir was resumed. Ten

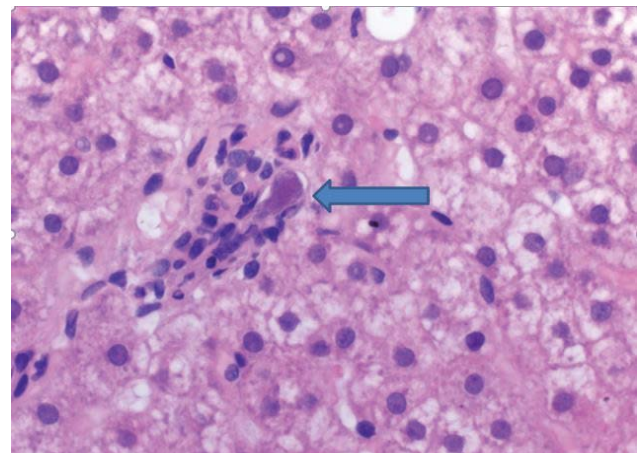


Figure 1: Liver core biopsy; High power view shows hepatocytes surrounding a small edge of portal tract with one enlarged endothelial cell showing CMV viral cytopathic effect with eosinophilic intranuclear inclusion, morphologically consistent with CMV infection).

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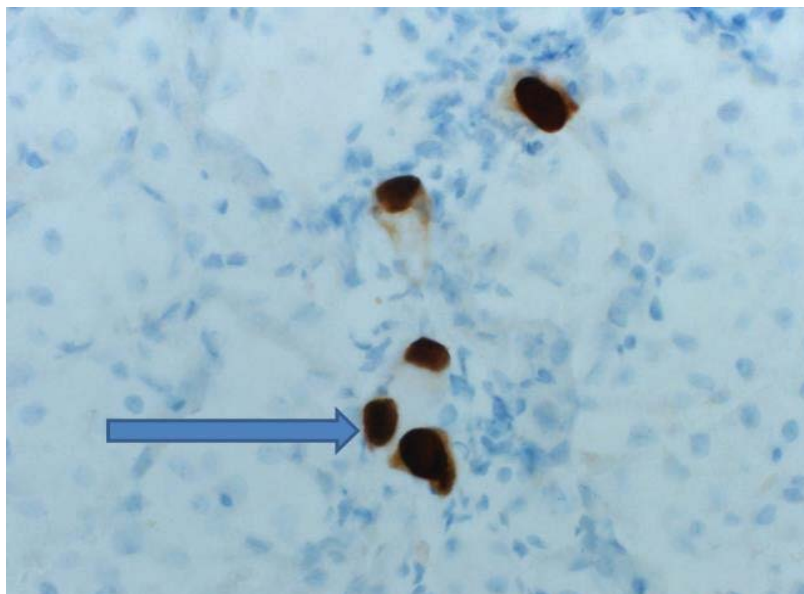


Figure 2: Immunohistochemistry for CMV was positive; high power view shows dark brown staining in the infected cells confirming the diagnosis.

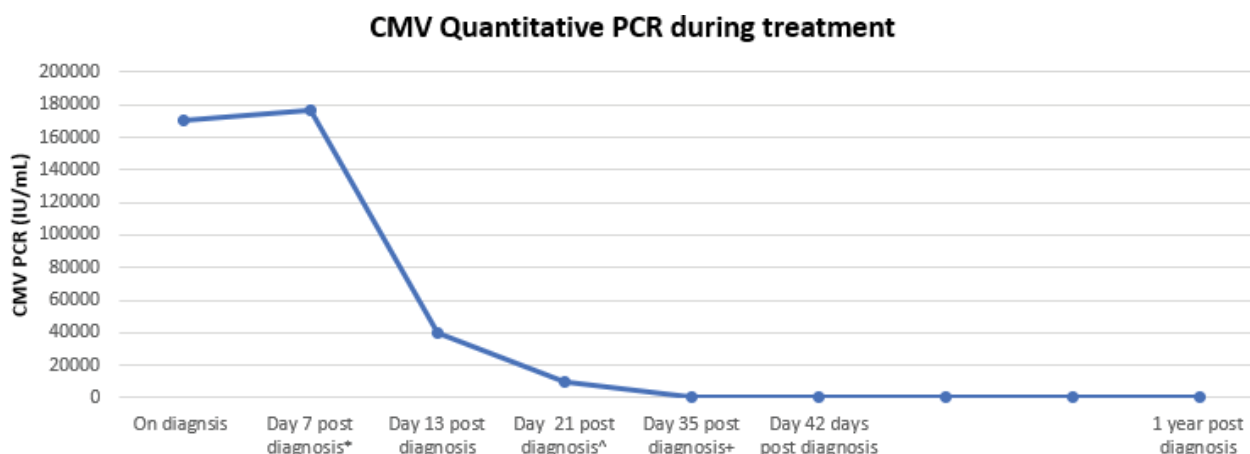


Figure 3: CMV Quantitative PCR during treatment

* High dose intravenous ganciclovir was started.

^ The Patient was shifted to oral valganciclovir.

+ The patient developed neutropenia. Valganciclovir was stopped and high dose intravenous ganciclovir was started again.

Case No.	Transplanted organ	Infection type	Resistance gene UL 97/UL 54	Mutation UL97/ UL54	High dose ganciclovir therapy	Reported Leukopenia (Yes/No)	Time to viremia clearance a
Case 1 (11)	Kidney -Pancreas	Colitis	UL 97/-	A594T/-	Yes	No	21 days
Case 2 (12)	Kidney	Duodenitis	UL97/-	-	Yes	Yes	173 days ^b
Case 3 (13)	Kidney	Colitis	UL97/UL54	C603W/T503I	No ^c	-	90 days

Table 1: Cases reported regarding resistant CMV disease in solid organ transplant

a, counted from the time of starting high dose ganciclovir or valganciclovir

b, in-between, the patient received Valganciclovir.

c, the patient was treated with high dose valganciclovir

days after stopping valganciclovir, absolute neutrophils count improved to 1.2 103/ μ L (total WBC count 1.7 103/ μ L). The patient finished total six weeks of treatment counted from the first day of high dose of the

Intravenous ganciclovir. Cytomegalovirus PCR was followed closely, and it was undetectable since week five of treatment and continued to be negative up to one year post treatment (Figure 3).

Discussion

Cytomegalovirus is a double stranded DNA virus. It has four copies of mRNA with a capsid protein and an envelope made of lipoprotein [1]. Clinical manifestation of cytomegalovirus can range from infectious mononucleosis symptoms to significant systemic disease [2]. CMV disease is a combination of clinical manifestations of organ involvement and documentation of CMV presence in the tissue by histopathology, immunohistochemistry, DNA Hybridization or rapid culture [3]. Risk factors for acquiring resistant CMV include inadequate dosage of prophylactic Valganciclovir, exposure to antiviral treatment for prolonged period, high immunosuppressive therapy and a transplant recipient being negative for CMV serology while the donor is positive [4].

Ganciclovir is a guanine nucleoside analog. Its activity against CMV is due to a phosphorylation process by a protein kinase phosphotransferase UL97, a viral coded enzyme, which converts ganciclovir to monophosphate. Then, the monophosphate form will be converted to ganciclovir triphosphate by a cellular enzyme which attacks the viral DNA polymerase UL 54 [5]. Mutation in the UL97 phosphotransferase gene or the UL54 polymerase gene can lead to Ganciclovir resistance [6]. M460V/I, H520Q, C592G, A594V, L595S and C603W, are recognized UL97 kinase mutations [7]. Foscarnet and Cidofovir are anti-Cytomegalovirus medication which can overcome Ganciclovir resistance due to UL97 kinase mutation [8]. However, nephrotoxicity is a known side effect for both [9,10].

There are few cases reported regarding resistant CMV disease in solid organ transplant which are treated successfully with high dose ganciclovir (**Table 1**) [11-13]. Up to our knowledge we are reporting the first case of resistant CMV hepatitis in solid organ transplanted patient treated with similar approach. The success of high dose ganciclovir in treating resistant CMV virus is possibly due to presence of UL 97 or UL 54 gene mutation with low resistance to ganciclovir. So a high dose of ganciclovir may overcome this resistance [4]. Our patient was successfully treated with a high dose ganciclovir. His follow up showed clearance of the viremia and normalization of the liver enzymes.

The clinical course of the patient was complicated by neutropenia which was most likely attributed to the valganciclovir. This complication was not seen while the patient was on high dose ganciclovir. Instead, neutropenia improved when the patient was shifted back again to the high dose ganciclovir. A previous study compared efficacy and safety of valganciclovir versus oral ganciclovir for cytomegalovirus disease prevention showed lower incidence of neutropenia with oral ganciclovir [14]. However, our patient was on Intravenous ganciclovir and whether it has similar effect on neutropenia or not needs further studying.

Conclusion

The risk of using nephrotoxic medication in kidney transplant patients makes the decision of treating resistant cytomegalovirus strain

difficult. The limited options of antiviral medication, with safe renal profile, in treating resistant CMV contributes to this difficulty. So, an alternative treatment strategy is needed specially for patients who are at higher risk of developing renal impairment. High dose of intravenous ganciclovir can be an alternative to Foscarnet and Cidofovir in treating UL97 mutated Cytomegalovirus infections, especially in kidney transplanted patients where nephrotoxic medications are avoided. To provide better evidence, further randomized control trials are needed to assess the efficacy and safety of high dose intravenous ganciclovir versus other treatment modalities.

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