DOI: 10.15386/cjmed-587

CYTOMEGALOVIRUS INFECTION IN IMMUNOSUPPRESSED PATIENTS AFTER KIDNEY TRANSPLANTATION

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Abstract

The first kidney transplantation was performed in 1951 and ever since then living donor transplantation became a more and more important solution for patients with end-stage renal disease (ESRD).

Renal transplantation is a life-saving procedure. Morbidity and mortality on waiting-lists are strongly correlated with the time of dialysis and end-stage renal disease is one of the most important causes of death; this is the reason why transplantation has to be performed as soon as possible in order to reduce the time of dialysis.

Once the transplantation is performed, a number of complications may occur in post-transplant evolution, the most important of which is rejection.

The rejection may appear through several mechanisms, but one of the most frequent causes of rejection is cytomegalovirus (CMV) infection. It is very important to have a precocious and fast diagnosis of CMV infection in order to maintain the functionality and survival of the graft. PP65 CMV antigenemia has proven its effectiveness in detecting and monitoring the CMV infection in transplanted patients.

In the laboratory of the Clinical Institute of Urology and Renal Transplantation (ICUTR) of Cluj Napoca the CMV infection is evidenced by two methods: PP65antigenemia and IgM antibody identification by chemiluminiscence.

Keywords: kidney transplantation, cytomegalovirus infection

Introduction

CMV infection is common even in the general immune-competent population, 50-80% of the healthy adult population being infected with CMV [1]. In immunocompromised patients, due to the transplantation procedure, the CMV infection rate is even higher, being an important cause of morbidity and mortality [2].

The risk of CMV infection depends heavily on the serological status of the donor (D) and of the recipient (R), with a high risk to D+/R-, D+/R+ combinations, but with a very high risk of developing CMV infections that are highly severe to the D+/R- combination [2].

The ability of the transplanted patient to eradicate CMV infection depends on several issues such as the type of immunosuppressive therapy received, the type of condition that has resulted in ESRD, or the number of MHC-missmatches as of the time of transplantation [2].

Diagnostic techniques

The CMV infection diagnosis can be performed by several methods [3-5]: antigen identification of CMV-infected fibroblasts, complement fixation test, ELISA test, agglutination Latex, by staining immunoperoxidase,

Manuscript received: 21.09.2015
Accepted: 25.10.2015
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determination of IgM and IgG immunoglobulins against CMV, antigenemia (65-kD lower matrix phosphoprotein, structural leukocyte protein) and DNA-CMV (PCR technique).

Transmission of CMV infection and the associated risk of infection as compared to other diseases

The probability of transmission in transplanted patients is variable depending on type of infection: 15-30% for CMV and 25-30% in pediatric, but 0-5% in adults for EBV. For HIV, the risk of transmission is 2-3% for all donors, but for high-risk donors we have up to 50% risk of transmission. The rest of infections (HBV, HCV, HTLV, malignancies etc) have a risk between 1-10% [6].

In terms of mortality, we have 100% for HIV transplanted infected patients, 25% in pediatric patients, but 1-2% in adults for EBV and 20-25% for CMV [6].

Methods of transmission of CMV infection

CMV infection can be transmitted by: exposure to maternal blood, secretions from the vagina-cervical or breast milk, contact in communities of children (kindergartens, schools), sexual transmission, direct contact between adults, blood transfusion, organ transplantation [7,8].

Mechanisms of occurrence of CMV infection

CMV infection can be: primary infection **(D+/R- or D-/R-),** reactivation (latent endogen virus) (**D-/R+ or D+/R+),** super infection **(D+/R+).**

Direct effects of CMV infection

CMV infection may progress as a primary infection, but it may also develop into a latent CMV which due to the immunosuppression therapy for transplant is activated in tissues and serum and thus CMV disease appears [9,10].

CMV disease can have direct effects when the virus can be identified in peripheral blood or by organ biopsy and is constituted by the so-called CMV syndrome [11]. The symptoms in CMV syndrome are: fever, malaise, myalgia, arthralgia, anorexia [11].

CMV tissue invasion can produce: pneumonia (severe in lung transplant patients), hepatitis (medium to severe), encephalitis, retinitis, nephritis, myocarditis, pancreatitis [11].

CMV effects on the gastrointestinal tract

CMV infection can produce many effects on the gastrointestinal tract: diffuse inflammation, functional alterations, hemorrhage, ulcers/perforations, nausea, vomiting, dysphagia, CMV gastritis, ileus, CMV hepatitis (especially in liver transplant patients), pancreatitis, especially in patients with pancreatic transplant [3,12].

CMV associated hematologic abnormalities

Hematologic changes are: leucopenia, thrombocytopenia, occurrence of atypical lymphocytes [3].

CMV infection is associated with rejection in different types of transplantation: acute rejection in recipients of renal allografts (CMV identified in approx. 50% of biopsies where the increased risk of atherosclerotic changes in the small arterioles can be distinguished) [12], vanishing bile duct syndrome after liver transplantation [13], rejection after heart transplant [14].

Indirect effects of CMV infection

CMV infection can produce indirect effects in liver: CMV infection associated graft lesions [15,16], hepatic artery thrombosis [9,17], rejection in patients co-infected with B or C viral hepatitis [18,19]. In kidney, the indirect effects can be: interstitial nephritis [20,21], renal artery stenosis or thrombotic microangiopathy [23,24].

Strategies for preventing CMV infection

CMV infection prevention can be achieved in two ways: Pre-emptive therapy and prophylaxis.

Pre-emptive therapy (before transplantation) is made by suppression of viral replication after viral load determination and continued until its negativity [24].

The advantage of pre-emptive therapy is effectiveness in the prevention of CMV disease development, while among the disadvantages we have the necessity to perform diagnostic tests weekly (pp65, DNA-CMV) in order to identify the moment of CMV infection appearance, it only prevents the occurrence of CMV disease but does not prevent CMV infection, with the possibility of indirect effects on CMV infection, and it is more expensive than prophylaxis [25].

Prophylactic therapy is ideally done by administering an anti-viral therapy right after transplantation, highly efficient, non-toxic, easier to administer and not very costly, to all (or groups with a greater risk of) kidney and/or pancreas graft recipients [24].

The advantages of prophylactic therapy are very low incidence of CMV disease, reduced indirect effects of CMV disease and reduced morbidity from infection. It can also prevent infection with HHV-6, HHV-8 and EBV and is not necessary weekly monitoring. The disadvantages of prophylactic therapy are the exposure to antiviral agents with the possibility of increased toxicity and a high risk of resistance to therapy [25].

There have been several meta-analyses and trials to compare pre-emptive treatment to the prophylaxis in CMV infection, and the results showed that pre-emptive treatment does not prevent the indirect effects of CMV infections, it has similar efficacy in preventing the occurrence of CMV disease, but does not reduce incidence of opportunistic infections and mortality, as prophylaxis does [25,26].

Prophylaxis reduces the risk of mortality in CMV infection and disease in comparison with placebo treatment or without a treatment: with 39% the risk of CMV infection, with 58% the risk of CMV disease and with 74% the risk of mortality all reported to placebo or no treatment [27].

KDIGO guides recommend that the recipients of a renal graft (unless both the donor and the recipient have a negative CMV serology) should get prophylaxis for CMV infection with ganciclovir or valganciclovir for at least 3 months after transplantation and for 6 weeks after the treatment with anti-lymphocytes T antibodies [2].

International Consensus Guidelines state that both pre-emptive strategies and prophylaxis are viable solutions to prevent CMV disease. For patients at high risk (D+/R-) both prophylaxis and pre-emptive therapy are recommended after renal or liver transplantation [29].

One of the biggest problems in terms of pre-emptive therapy is that it does not prevent the indirect effects of CMV infection, including effects on patient survival [29].

Duration of prophylaxis in D+/R- patients after liver, heart and pancreatic transplantation, should be generally between 3 to 6 months. The decision to use prophylaxis 3, 6 months or more may depend on the level of immunosuppression, including the use of antilymphocytic antibodies for immunosuppression induction. When used for prophylaxis, the usual dose of valganciclovir is 900 mg/day versus the treatment, when 900 mg/2 days are administered, but the dose should be adjusted based on the renal function. The antiviral medication dosage should be based on standard algorithms dosage and adjusted depending on the renal function. Minidose strategies (eg valganciclovir 450 mg/day with a normal renal function) are not recommended [29].

It is important to use appropriate doses of ganciclovir and valganciclovir. The use of improper doses can reduce efficiency and can promote resistance. For a CMV disease that is not severe, as a first-line therapy in adults, the oral intake is recommended, of valganciclovir 900 mg/12h or ganciclovir IV 5 mg/kg every 12 hours. The treatment with twice daily administrations of valganciclovir or ganciclovir IV every 12 hr should continue until the complete eradication of infection. Secondary prophylaxis with 900 mg valganciclovir daily for 1 to 3 months can be recommended particularly in patients with an increased risk [29].

Reducing the dose of antiviral therapy should be considered in cases of severe CMV disease in patients who do not respond to treatment, in patients with a high viral load and leucopenia. The return to the initial immunosuppressive therapy can be considered only when obtaining an adequate clinical and viral response [29].

Conclusions

The CMV infection is the most important infectious cause of rejection. That's why we have to avoid its appearance or, in case of appearance, a correct diagnosis and treatment is necessary as soon as possible in order to avoid the consequences of CMV infection.

CMV infection may be prevented by prophylactic therapy and early diagnosis can be made by pp65 antigenemia or DNA-CMV viral load. Also, a correct treatment with adjusted doses and the continuity of the treatment until infection eradication is very important in order to avoid CMV disease and antiviral therapy resistance.

Acknowledgement

This paper was published under the frame of European Social Found, Human Resources development Operational Programme 2007-2013 project no. POSDRU/159/1.5/138776.

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