Cytomegalovirus Disease in Renal Transplant Recipients: A Single-Center Experience

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Objectives: **Cytomegalovirus is the most common viral infection following kidney transplant, with overall frequencies of 50% to 80% for the infection and 20% to 60% for cytomegalovirus disease.**

Materials and Methods: **We retrospectively analyzed the medical records of 689 kidney transplant recipients at Jeddah Kidney Center in the Kingdom of Saudi Arabia between January 2000 and December 2005 for cytomegalovirus infection and disease. We examined the source of the donated kidneys (deceased versus living donor), the cytomegalovirus serostatus of the donor and recipient, the immunosuppressive protocol, the presence of cytomegalovirus prophylaxis, the clinical presentation of acute cytomegalovirus disease, the patient's response to treatment, and the effect of cytomegalovirus disease on graft and patient survival.**

Results: **Of 689 kidney transplant recipients, 25 (3.6%) had acute cytomegalovirus disease. All 25 patients had cytomegalovirus IgG positive/IgM negative test results prior to transplant. We noticed 2 distinct groups of patients: the first group included 9 patients with cytomegalovirus syndrome, 6 of whom received cytomegalovirus prophylaxis with ganciclovir. All patients in this group had low cytomegalovirus viral loads on polymerase chain reaction, mild disease, and responded to treatment with complete recovery and no adverse effects with respect to themselves or their grafts. The second group included 16 patients with invasive cytomegalovirus disease, 3 of whom received cytomegalovirus prophylaxis. All patients in this group had very high cytomegalovirus viral loads on polymerase chain reaction. Thirteen patients in this group (81%) responded to treatment with full recovery, and normal graft function was maintained in 10 (62%). Of the original 16 patients in this group, 3 (18.8%) died from cytomegalovirus disease and its complications.**

Conclusions: **We report a low incidence (3.6%) of cytomegalovirus disease at our center. Cytomegalovirus prophylaxis was associated with a milder form of the disease. At our center, treatment of invasive cytomegalovirus disease produced a patient survival rate of 81% and a graft survival rate of 62%.**

Key words: *CMV, Prophylaxis, Ganciclovir, Infection, Kidney*

Although symptomatic infection with cytomegalovirus (CMV) in the general adult population is usually mild, the virus produces severe symptoms in immunocompromised patients. CMV is the most common viral infection following kidney transplant. In general, the dosage, duration, agents used, intensity of the immunosuppressive regimen, and the CMV antibody status (seronegative vs seropositive) in both the donor and the recipient before transplant, all determine the risk of CMV in transplant recipients. The overall frequency of CMV infection after kidney transplant varies from 50% to 80% of patients, whereas CMV disease is observed in 20% to 60% of recipients [1]. CMV infection in kidney transplant patients may be symptomatic or asymptomatic, but CMV disease refers to symptomatic acute CMV infection and can be further divided into CMV syndrome and invasive CMV disease [2]. Diagnosis of CMV in transplant recipients is crucial. Enzyme-linked immunosorbent assay is useful for pretransplant serologic screening and to document seroconversion, but it is less useful for diagnosing CMV disease. Detection

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of the CMV pp65 antigen and CMV DNA by polymerase chain reaction (PCR) is the preferred means of diagnosing CMV disease associated with viremia [3].

Subjects and Methods

A retrospective single-center study was performed. The study population was composed of kidney transplant recipients from our center and other centers but who were followed up at our center between January 2000 and December 2005. Data were collected from the medical records of 689 kidney transplant recipients. We examined the source of the donated kidneys (deceased versus living donor), the CMV serostatus of the donor and recipient, the immunosuppressive protocol, the presence of CMV prophylaxis, the clinical presentation of acute CMV disease, the patient's response to treatment, and the effect of CMV disease on graft and patient survival.

Results

Kidney transplant recipients at our center are usually screened for CMV infection when there is any clinical suspicion of CMV disease. Of 689 patients, 25 (3.6%) developed acute CMV disease. Serologic testing showed that all patients had CMV IgG positive/IgM negative results prior to transplant. CMV serostatus of the corresponding kidney donors was positive in 9 living-related donors and unknown in 16 donors (13 living-unrelated and 3 deceased). All CMV patients (D+/R+) were given CMV prophylaxis in the form of parenteral ganciclovir followed by 3 months' treatment with oral ganciclovir, or valacyclovir, or acyclovir. Immunosuppressive medications included prednisolone, cyclosporine, and azathioprine in 10 patients, and prednisolone, cyclosporine, and mycophenolate mofetil in another 15 patients. Five patients received antithymocyte globulin either as induction or as antirejection therapy.

We noticed 2 distinct groups of patients, the first group (the CMV syndrome group) was composed of 9 patients presenting with fever, malaise, and leucopenia. The serologic test results for this group after transplant were the same as they were before transplant, that is, CMV IgG positive/CMV IgM negative. Diagnosis of CMV disease was confirmed by CMV PCR test (AMPLICOR, Roche Molecular Systems, Basel, Switzerland) with low viral counts of approximately 536 to 3070 copies/mL. Six patients in this group received CMV prophylaxis after transplant. All patients in this group responded completely after 2 weeks of treatment with intravenous ganciclovir, with no adverse effects on the grafts or the patients. The second group (the invasive CMV disease group) was composed of 16 patients presenting with fever, pancytopenia, hepatitis, and graft dysfunction; 5 patients also had pneumonitis. Serologic testing of CMV IgM was positive in 9 patients and negative in 7 patients (no antibody response). The CMV-PCR test was strongly positive in all patients, with viral counts exceeding 850 000 copies/mL in several of the patients. Only 3 patients in this group were given CMV prophylaxis after transplant. The patients were given intravenous ganciclovir and their immunosuppressive medications were reduced; only a few patients (especially those with pneumonitis) required intensive supportive therapy consisting of admission to the intensive care unit, inotropic support, and mechanical ventilation. Thirteen patients in this group (81%) responded to treatment. Full recovery (ie, normal graft function) was observed in 10 patients (62%), while 3 patients (18.8%) survived invasive CMV disease but lost their graft and returned to dialysis. Of the original 16 patients in this group, 3 (18.8%) died from CMV disease and its complications.

Discussion

CMV disease following renal transplant continues to be a major clinical problem with significant morbidity and mortality. The overall frequency of CMV infection after kidney transplant varies from 50% to 80% of patients, whereas CMV disease is observed in 20% to 60% of recipients [1]. We report a low prevalence of CMV disease (3.6%) at our center from January 2000 to December 2005 in a population of 689 kidney transplant recipients. Diagnosis of CMV in our patients was based on PCR testing (which is quite sensitive for CMV) and monitoring of its viremia [3]. All patients who developed CMV disease were CMV seropositive prior to transplant. Nine kidney donors were seropositive, and 16 had an unknown serology. Universal CMV prophylaxis was given to all (D+/R+) kidney transplant recipients taking conventional immunosuppressive agents as well as to all seropositive recipients receiving antithymocyte globulin, either as induction or as antirejection therapy [4]. As recommended in other studies [5, 6, 7], we used intravenous ganciclovir at a dosage of 5 mg/kg twice daily adjusted to the glomerular filtration rate for the first 2 weeks, followed by high-dose oral acyclovir or valacyclovir

or ganciclovir (whichever was available at that time) for a total of 12 weeks.

CMV disease should be suspected in any kidney transplant recipient who presents during the first few months after transplant with symptoms of fever, malaise, and a finding of leucopenia or elevated liver enzymes [8]. Renal transplant recipients may not respond to active infection by producing CMV IgM antibodies; this was observed in the first group of our patients with CMV syndrome and in 7 out of 16 patients in the second group with invasive CMV disease. Techniques for rapidly diagnosing CMV infection include shell vial culture, pp65 antigenemia assay, PCR, and the hybrid-capture RNA-DNA hybridization assay for qualitative detection of CMV-PCR [9]. The best approach for diagnosing CMV disease is the CMV-PCR test, as long as the clinician interprets the result with respect to the clinical scenario.

Diagnoses of CMV disease in our patients were based on a PCR test. The highest viral loads (as measured by PCR) are most often associated with invasive tissue disease; the lowest loads are most often seen in patients with asymptomatic CMV infection; and intermediate viral loads are most frequently seen in patients with CMV syndrome [10]. This was demonstrated in our patients: the first group (CMV syndrome group) had low to intermediate viral loads, while the second group (invasive CMV disease group) had high to very high viral loads. At the time of this writing, the only validated treatment for renal transplant recipients with documented CMV disease is intravenous ganciclovir at a daily dosage of 10 mg/kg/d (5 mg /kg twice per day) adjusted to the glomerular filtration rate for at least 14 days [11]. Our patients with CMV syndrome responded to intravenous ganciclovir with no adverse effects from the disease or from the medication. Thirteen of 16 patients with invasive CMV disease survived the disease when treated with ganciclovir; however, 3 patients lost their grafts, probably as the result of direct and indirect effects of CMV infection on the graft [8]. In addition to directly attributable morbidity, CMV also may have an immunomodulatory effect, and active CMV disease has been found to be an independent risk factor for developing other infectious complications [12]. Three of our patients with invasive CMV disease died of severe intractable infectious complications.

In conclusion, we report a low incidence of CMV disease (3.6%) at our center. Universal CMV prophylaxis was associated with a mild form of the disease in our patients. Treatment of invasive CMV disease at our center demonstrated patient and graft survival rates of 81% and 62%, respectively.

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