

The Incidence of Cytomegalovirus Infection in Lung Transplant Recipients under Universal Prophylaxis with Intravenous Ganciclovir

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The best strategy for control of cytomegalovirus (CMV) infection in lung transplant patients is still not determined. The aim of this study was to document the incidence of CMV infection in a cohort of lung transplant recipients under universal prophylaxis with intravenous ganciclovir. All patients received immunosuppressive regimens consisting of cyclosporine, azathioprine, and prednisone. Regardless of CMV serostatus, intravenous ganciclovir was prescribed for every patient in the first 3 months post-transplantation. CMV infection was defined as the detection of CMV pp65 in leukocytes. Eighty-two lung transplant patients were included over a 5-year period. The incidence of CMV infection in the first year post-transplantation was 68.3%, occurring after a median length of 114 days (range, 26-343 days). This study revealed a high incidence of CMV infection in the first year following lung transplantation despite prolonged universal ganciclovir prophylaxis.

Key-Words: Cytomegalovirus, antigenemia, lung transplantation, ganciclovir, prophylaxis.

Cytomegalovirus (CMV) is a major concern in immunosuppressed patients, particularly in the context of solid organ transplantation (SOT). The incidence of CMV infection and disease is higher in lung transplant recipients than in other SOT patients, with reported rates of 54% to 92% in the absence of CMV prophylaxis [1,2]. Based on these findings, most preventive approaches to date have involved universal prophylaxis with ganciclovir in which all patients receive prophylaxis for a pre-determined duration. However, this strategy is very controversial. Data against universal prophylaxis include drug-related toxicities (mainly hematological), costs, and necessity of vascular accesses. In addition, it has been reported that 0%-13% of transplant patients receiving ganciclovir develop secondary resistance to this drug [3]; rates as high as 27% has been reported in D⁺/R⁻ lung transplant recipients [4]. Moreover, the diagnosis of resistance is not easy, requiring modern technologies, and few therapeutic options are available for the treatment of ganciclovir-resistant CMV. The aim of this study was to determine the incidence of CMV infection 1 year after lung transplantation in a population of patients submitted to universal prophylaxis with intravenous ganciclovir over a 5-year period.

Materials and Methods

This retrospective cohort study was conducted in Santa Casa Complexo Hospitalar, a 1,200-bed Brazilian tertiary hospital and reference center for SOT in South America. Patients submitted to lung transplantation between March

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1999 and February 2004 were eligible for study. All patients received triple immunosuppressive regimens consisting of cyclosporine, azathioprine, and prednisone. A protocol of universal prophylaxis with intravenous ganciclovir was adopted, regardless of CMV serostatus, as follows: 10 mg/kg/daily for the 3 weeks post-transplantation, followed by 5 mg/kg/daily for the weeks 4 to 12. CMV infection was defined as the detection of CMV pp65 in leukocytes using monoclonal antibodies (Clonab-Biotest, Germany) [5], and the results of the antigenemia test were reported as the number of positive cells per 10⁵ circulating granulocytes. Patients were monitored weekly for the presence of pp65 antigenemia between weeks 3 and 12 following transplantation (the period of higher risk for CMV infection), and then every 15 days in the months 4 to 12 post-transplant. Additional testing was performed according to clinical suspicion. Due to the absence of data related to CMV infection, patients who died in the first month following lung transplantation were excluded from the analysis. Descriptive statistics were used to summarize the data.

Results

During the period of study, 106 lung transplants were performed in our institution. Twenty-four patients (22.6%) were excluded due to the occurrence of death in the first month following transplantation, resulting in 82 patients for analysis. Most of these patients were male (65.9%), and mean age was 51.2 years-old (range, 7-72 years-old). Donor source was cadaveric-related in 92.7%.

The incidence of CMV infection in the first year post-transplantation was 68.3% (n=56). For these patients, median number of positive cells was 11.4/10⁵ granulocytes (range, 1/10⁵-1,096/10⁵ cells). Most of the patients (53.6%) had counts higher than 10 cells/10⁵ granulocytes. The first positive test following transplantation occurred after a median length of 114 days (range, 26-343 days). No difference was observed regarding gender, age, and donor status (cadaveric- or living-

related) among patients who developed a positive CMV antigenemia test and those who did not.

The overall mortality in the first year after transplantation was 37.8% (n=40), and no difference in the mortality rate was observed when patients were stratified according to the occurrence of CMV infection (p=0.204) or to the number of positive infected granulocytes (p=0.128 for counts higher or lower than 10/10⁵ cells).

Discussion

Our results showed a high incidence of CMV infection after lung transplantation (68.3%), despite a policy of prolonged universal prophylaxis with intravenous ganciclovir. Similarly, previous studies have revealed that antiviral prophylaxis does not avoid but postpone the occurrence of CMV infection [6-12]. Nevertheless, this delay may be deleterious. Following cessation of prophylaxis, the virus may then be detected in a time when the typical patient is relatively well and undergoing outpatient visits, potentially leading to a late diagnosis with associated higher viral loads [13]. In addition, treatment of late CMV infection with intravenous ganciclovir may produce a tardy response of viral load due to resistant virus within the population. Such issues do not arise with preemptive therapy since the duration of treatment is much shorter than that required to select for resistance [14]. The pp65 antigenemia test is a very fast, sensitive and specific method for the diagnosis of CMV infection in SOT patients [15-17]. The probability of CMV disease in a patient with a negative antigenemia test is close to zero [15]. In our institution, the experience with pp65 antigenemia test in renal transplant recipients as a preemptive tool revealed an incidence of CMV infection and disease of 60% and 38%, respectively, in the first 3 months post-transplant [18]. At this moment, preemptive therapy is strongly being considered for lung transplant recipients in our medical center as well.

Although there is a paucity of strong data on the efficacy and safety of preemptive therapy compared with those of universal prophylaxis in lung transplant recipients [19], some centers have followed a preemptive approach to the management of these patients, which has been shown to be safe and effective [20-22]. Theoretically, a preemptive approach might be expected to be associated with lower rates of resistance, because antiviral therapy is specifically targeted to patients considered to be at risk (rather than to all patients) [3]. Given the availability of the pp65 antigenemia test and the limitations of the anti-CMV drugs currently existing, preemptive therapy seems to offer the best way to minimize unnecessary drug exposure while ensuring that CMV disease is controlled and allowing cost-effective use of limited resources [13]. Furthermore, antiviral prophylaxis was not shown to reduce mortality or the incidence of bronchiolitis obliterans syndrome following lung transplantation [12,23], which are major concerns.

In conclusion, this study revealed a considerably high incidence (68%) of CMV infection in the first year following

lung transplantation despite prolonged universal prophylaxis with intravenous ganciclovir. We believe that universal prophylaxis should be reserved to the group of patients under higher risk of CMV infection, i.e. those with D⁺/R⁻ serostatus. For the others, the use of preemptive therapy based on a sensitive test such as pp65 antigenemia may be a reasonable option. Randomized clinical trials are expected to answer this question.

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