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Incidence, Risk Factors, and Outcome of Cytomegalovirus Infection and Disease in Patients Receiving Prophylaxis with Oral Valganciclovir or Intravenous Ganciclovir after Umbilical Cord Blood Transplantation

Pau Montesinos,[1] Jaime Sanz,[1] Susana Cantero,[1] Ignacio Lorenzo,[1] Guillermo Martín,[1] Silvana Saavedra,[1] Javier Palau,[1] Mónica Romero,[1] Alberto Montava,[1] Leonor Senent,[1] Jesús Martínez,[1] Isidro Jarque,[1] Miguel Salavert,[2] Juan Córdoba,[3] Lola Gómez,[3] Shirley Weiss,[1] Federico Moscardó,[1] Javier de la Rubia,[1] Luis Larrea,[4] Miguel A. Sanz,[1] Guillermo F. Sanz[1]

There is no information on the efficacy and safety of anticytomegalovirus (CMV) prophylaxis with intravenous ganciclovir or oral valganciclovir after unrelated cord-blood transplantation (UCBT). This issue was addressed in 151 adults (117 CMV-seropositive) undergoing UCBT at a single institution. The first 38 CMV-seropositive recipients were assigned to receive prophylactic ganciclovir, and the next 79 were given valganciclovir after engraftment. The cumulative incidence (CI) of CMV infection and disease was similar in patients receiving valganciclovir or ganciclovir (59% versus 55%, $P = .59$; and 9% versus 18%, $P = .33$, respectively). The toxicity profile and CI of nonrelapse mortality (CMV) and infection-related mortality did not differ between drugs. Patients receiving valganciclovir required fewer visits to the day hospital ($P = .04$). The CI of CMV infection and disease in 34 CMV-seronegative recipients was 12% and 6%, indicating that tight CMV monitoring is mandatory in this subset. The recipient's CMV serostatus, acute and extensive chronic graft-versus-host disease (aGVHD, cGVHD) were the main risk factors for CMV infection, and aGVHD for CMV disease. This study suggests that prophylaxis with oral valganciclovir is as safe and effective as intravenous ganciclovir for preventing CMV infection and disease after UCBT, but valganciclovir reduces the use of hospital resources.

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INTRODUCTION

The introduction of ganciclovir, a potent anticytomegalovirus (CMV) agent, and the rapid initiation of treatment at the earliest signs of infection based on detection assays, such as DNA polymerase chain reaction (PCR) or pp65 antigenemia (pp65 Ag), have permitted major advances in the prevention and treatment of CMV disease after allogeneic hematopoietic stem cell transplant (HSCT) [1,2]. However, despite this progress, CMV infection and disease remain a significant cause of morbidity and mortality [1,2]. Patients receiving unrelated cord blood transplantation (UCBT) represent a subset with a high risk of CMV infection and disease because of poor immune reconstitution [3]. Nevertheless, the incidence and outcome of, and risk factors for, CMV infection and disease after UCBT have been scarcely addressed [4-8].

The knowledge of risk factors predicting CMV infection and disease, such as the patient's and donor's CMV serologic status [9-11] unrelated donor [12]

From the [1]Department of Hematology; [2]Division of Infectious Diseases; [3]Department of Microbiology, Hospital Universitario La Fe, Valencia, Spain; and [4]Centro de Trasfusión de la Comunidad Valenciana, Valencia, Spain.

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Correspondence and reprint requests: Pau Montesinos, MD, Department of Hematology, University Hospital La Fe, Avenida Campanar 21, 46009 Valencia, Spain (email: montesinos_pau@gva.es).

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graft-versus-host disease (GVHD) [13], and T cell depletion [4,10], allows the clinician to select the best preventive strategy based on the patient's risk status. Strategies in high-risk patients include preemptive therapy with intravenous ganciclovir as soon as they become positive for CMV in the blood [14,15]; or intravenous ganciclovir prophylaxis initiated in all patients at the time of engraftment and continued until day 100 after transplant [16,17]. The only randomized study comparing both preventive strategies showed a lower incidence of CMV infection and a similar incidence of disease and survival, but a higher incidence of neutropenia and fungal and bacterial infections in patients under prophylaxis [18]. Preemptive therapy with ganciclovir is the strategy used most frequently to reduce the incidence of CMV disease after allogeneic HSCT [2,19]. However, prophylaxis may be justified in patients with a very high risk of CMV infection and disease [1,2,11] such as CMV-seropositive recipients undergoing UCBT.

Valganciclovir, an oral prodrug of ganciclovir with excellent bioavailability [20,21], has a similar efficacy to intravenous ganciclovir for prophylaxis of CMV infection in organ-solid transplant recipients [22-24]. Early studies also showed a similar efficacy to intravenous ganciclovir as preemptive therapy in allogeneic HSCT recipients [25-28]. Oral valganciclovir has the potential to replace intravenous ganciclovir, making outpatient care possible, which should provide more comfort for the patient and reduce the use of hospital resources. Oral valganciclovir may be especially valuable when prophylaxis for CMV infection and disease is considered. Unfortunately, there is no information on the efficacy and safety of valganciclovir as prophylaxis after allogeneic HSCT.

This study aimed to evaluate and compare the efficacy, toxicity, and hospital resource use of prophylaxis of CMV infection and disease with intravenous ganciclovir or oral valganciclovir in 2 consecutive cohorts of CMV-seropositive adult patients undergoing UCBT at a single center. The rates of CMV infection and disease were also assessed in the group of CMV-seronegative patients, in whom prophylaxis comprised low-dose acyclovir. We also analyzed the characteristics, outcome, and risk factors for CMV infection and disease.

MATERIAL AND METHODS

Patients and Transplant Characteristics

From May 1997 to July 2008, 151 adults with hematologic malignancies underwent UCBT at Hospital Universitario La Fe, Valencia, Spain. All patients provided informed consent according to institutional guidelines. The transplant protocols were approved by the Research Ethics Board of the institution according to the Declaration of Helsinki. Patients undergoing UCBT with reduced-intensity conditioning (RIC) regimens were excluded from the study. Donor-recipient matching was based on low-resolution HLA typing for HLA-A and HLA-B, and high resolution for HLA-DRB1. Early-disease stage at UCBT was defined as chronic myelogenous leukemia (CML) in the chronic phase, acute leukemia in first or second complete remission (CR), myelodysplastic syndrome (MDS) untreated or in CR, and lymphoma in CR.

Preparative Regimens and GVHD Prophylaxis

The conditioning regimen comprised thiotepa (TT), busulfan (Bu), cyclophosphamide (Cy), and antithymocyte globulin (ATG) in 71 patients (47%) [29], of whom 32 received horse ATG (Lymphoglobulin®, Mérieux, Lyon, France) and 39 received rabbit ATG (Thymoglobulin®, Genzyme, Framingham, MA). The conditioning regimen comprised TT, Bu, fludarabine (Flu), and Thymoglobulin in 78 other patients (52%) [30]. One patient received Flu, TT, and Lymphoglobulin as preparative regimen.

Acute GVHD (aGVHD) prophylaxis comprised cyclosporine (CsA) plus prednisone in 79% of patients, and CsA plus mycophenolate mofetil (MMF) in the remaining 21%. aGVHD and chronic GVHD (cGVHD) were graded according to criteria published elsewhere [31,32].

Risk Stratification, Monitoring, and Diagnosis of CMV Infection and Disease

CMV serology from the mother or cord blood unit (CBU) and the recipient were assessed before UCBT. None of the CBU or mothers was positive for immunoglobulin M (IgM) antibody to CMV. The CBU was considered CMV seronegative regardless of the serostatus of the mother, and the risk stratification for CMV infection and disease was based only on the patient's CMV serostatus [33].

In CMV-seronegative (low-risk) patients, CMV surveillance analysis was not performed systematically. CMV surveillance monitoring of peripheral blood (PB) samples from CMV-seropositive (high-risk) patients was performed twice weekly from day 7 after transplant to day +100, every 15 days until day +180, monthly until day +365, and weekly for patients taking more than 15 mg daily of prednisone for cGVHD. CMV surveillance analysis was performed using pp65 Ag in PB leukocytes in the first 60 CMV-seropositive patients (51%), and plasma quantitative LightCycler-based PCR (LC-PCR; Roche Diagnostics GmbH, Mannheim, Germany) [34] in the next 57 patients (49%).

Diagnosis of CMV viremia was made in the presence of 1 or more positive pp65 Ag assay (>1 infected cell of 50,000 cells) or 1 or more positive PCR result