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Infections of the Central Nervous System after Unrelated Donor Umbilical Cord Blood Transplantation or Human Leukocyte Antigen–Matched Sibling Transplantation

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A B S T R A C T

We analyzed the incidence, clinical characteristics, prognostic factors, and outcome of central nervous system (CNS) infections in consecutive patients with receiving umbilical cord blood transplantation (UCBT) (n = 343) or HLA-matched sibling donor stem cell transplantation (MST) (n = 366). Thirty-four CNS infections were documented at a median time of 116 days after transplantation (range, 7 to 1161). The cumulative incidence (CI) risk of developing a CNS infection was .6% at day +30, 2.3% at day +90, and 4.9% at 5 years. The 5-year CI of CNS infection was 8.2% after UCBT and 1.7% after MST ($P < .001$). The causative micro-organisms of CNS infections were fungi (35%), virus (32%), *Toxoplasma* spp. (12%), and bacteria (12%). Fungal infections occurred in 11 patients after UCBT and 1 after MST and were due to *Aspergillus* spp. (n = 8), *Cryptococcus neoformans* (n = 2), *Scedosporium prolificans* (n = 1), and *Mucor* (n = 1). Except for 1 patient, all died from CNS fungal infection. Viral infections occurred in 9 patients after UCBT and 1 after MST and were due to human herpes virus 6 (n = 7), cytomegalovirus (n = 2), and varicella zoster virus (n = 1). CNS toxoplasmosis was diagnosed in 3 patients after UCBT and 1 after MST. Other pathogens were *Staphylococcus* spp, Nocardia spp, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis*. Twenty of the 34 patients (59%) died from the CNS infection. In multivariable analysis, UCBT and disease stage beyond first complete remission were independently associated with the risk of developing CNS infections. The 5-year overall survival was 19% in patients who developed a CNS and 39% for those who did not ($P = .006$). In conclusion, our study showed that CNS infections are a significant clinical problem after stem cell transplantation associated with poor survival. They were more frequent after UCBT compared to MST.

INTRODUCTION

Central nervous system (CNS) infections in patients undergoing allogeneic (allo) stem cell transplantation (SCT) represent an important cause of morbidity and mortality [1-5]. However, these infections have not been well characterized to date.

Most studies are focused on neurologic complications in general, including different causes such as infections, vascular events, and metabolic or immune-mediated disorders, among others [2,5,6]. In addition, the study population, SCT procedures, stem cell sources, underlying disease, and time of follow-up ranges widely through different studies [1,3,7]. It is, therefore, difficult to assess the real incidence of CNS infections after allo-SCT, and it is probably underestimated considering the fact that in autopsy studies, CNS infections were found in up to 15% of patients who died after SCT [8]. Moreover, data on long-term CNS infections (beyond 1 year) are limited because of the relatively short follow-up in most studies. In addition, little is known about the impact of the

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stem cell source on these complications. In fact, few studies have compared the incidence of infections in patients receiving unrelated umbilical cord blood transplantations (UCBT) compared with other transplantation modalities [9], and there are no specific data on CNS infections in these patients.

The main objective of this study was to analyze the incidence of CNS infections and describe their clinical characteristics in a large series of patients with hematologic diseases undergoing HLA-matched sibling donor stem cell transplantation (MST) or UCBT with a prolonged follow-up. A secondary objective was to investigate the risk factors for developing CNS infections and their influence on outcome.

PATIENTS AND METHODS

Eligibility Criteria

All consecutive adult patients with hematological diseases who underwent MST or UCBT at the Hospital Universitario La Fe between January 2000 and May 2014 were included in the study. The institutional review board approved the protocol and written informed consent was obtained from all patients according to the Declaration of Helsinki.

Data Collection

We retrospectively reviewed data of patients, transplantation procedures, and CNS infections that had been prospectively collected and recorded in a computerized database. All patients were evaluated by a neurologist, and the clinical charts were also reviewed for inconsistences and missing data.

Transplantation Procedures

Conditioning regimen

The conditioning therapy was according to institutional protocols, based on the patient's age, comorbidities and underlying disease. The conditioning regimen consisted of either a conventional myeloablative regimen or a reduced-intensity conditioning. The intensity of the conditioning regimen depended on the disease, performance status, and comorbidities of the patient, according to current protocols. Conditioning regimens for UCBT have been previously described in detail [10-12] and consisted of a combination of thiotepa, busulfan, cyclophosphamide or fludarabine, and antithymocyte globulin (ATG). For MST, except for 3 patients who received total body irradiation, all patients received busulfan combined with fludarabine [13,14] or cyclophosphamide [15] or a combination of melphalan with fludarabine [14]. Phenytoin prophylaxis was given to all patients receiving busulfan as part of the conditioning regimen.

Management of graft-versus-host-disease

For graft-versus-host disease (GVHD) prophylaxis, all patients received cyclosporine combined with either prednisone, methotrexate, or mycophenolate mofetil. Patients developing acute GVHD received high-dose methylprednisolone as initial therapy (2 mg/kg/day to 20 mg/kg/day) and ATG was used in refractory cases. Chronic GVHD was treated with prednisone (1 mg/kg/day). Details of dose and schedules have been reported elsewhere [10,11,16].

Supportive care

Supportive care followed institutional policies, as previously described [17]. Patients were nursed in high-efficiency particulate air–filtered rooms. A mold-active azole (itraconazole or voriconazole) was used during 6 months after UCBT and while on steroids for the treatment of GVHD in MST. Voriconazole levels were monitored. Prophylaxis against *Pneumocystis jiroveci* consisted of cotrimoxazole 2 days a week and maintained for a minimum of 1 year or until immunosuppressive therapy was stopped. Pentamidine was used if cotrimoxazole was contraindicated. All blood products were irradiated and leukocyte depleted. Cytomegalovirus (CMV)-seropositive patients received prophylaxis with either intravenous ganciclovir or oral valganciclovir. When a positive CMV PCR or pp65 Ag test was detected, pre-emptive first-line therapy was started with intravenous ganciclovir 5 mg/kg twice daily or oral valganciclovir 900 mg twice daily. Nonspecific intravenous immunoglobulin was administered at a dose of 500 mg/kg weekly until day +100 and then monthly within the first year of transplantation.

Definitions

CNS infection was defined as any infection of the CNS that occurred after the start of the conditioning regimen and before relapse or progression of underlying disease. The *onset of the CNS infection* was defined as the first day with neurological symptoms. Diagnosis of CNS infection was based on imaging, cerebrospinal fluid (CSF) examination, and microbiologic findings. They were classified in different categories according to the final diagnosis, which was made by a combination of clinical, radiologic, laboratory, and microbiologic findings and/or postmortem studies. In selected cases, the diagnosis required a biopsy of focal lesions. Invasive fungal infections were classified according to European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group revised definitions of 2008 [18]. Viral CNS infections were diagnosed with CSF virus DNA detection by PCR. Cases with negative CSF cultures were classified as "CNS infection not microbiologically documented" when clinical, imaging, and CSF characteristics strongly suggested a CNS infection. Cutaneous herpes zoster infections were not analyzed.

Statistical Analysis

Characteristics of patients receiving MST or UCBT were compared using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The probability of CNS infection was estimated by the cumulative incidence (CI) method (marginal probability) and for comparisons the Gray test was used [19,20]. For CI analyses, relapse and death without CNS infection were considered as a competing cause of failure. The Fine and Gray method for competing events was used for multivariable analysis using variables with a P value < .10 for each endpoint. Variables included in the model were transplantation type (MST versus UCBT), conditioning regimen (myeloablative versus reduced-intensity conditioning), diagnosis, age, gender, CMV serostatus, previous transplantation, and disease stage at transplantation. Relapse was the competing event for nonrelapse mortality (NRM), and death and relapse were competing events for CNS infections. Statistical analysis was conducted using R version 2.12.2 (The CRAN project) with packages, Design 2.3-0, prodlim v1.2.1 and cmprsk v2.2-2 12 [21]. Unadjusted time-to-event analyses were performed using the Kaplan-Meier estimate [22], and, for comparisons, the log-rank tests [23].

RESULTS

Patient, Transplantation, and Graft Characteristics

Patient, disease, and graft characteristics according to the type of transplantation are described in Table 1. Briefly, 343 patients underwent UCBT and 366 underwent MST.