Foscarnet – an alternative for cytomegalovirus prophylaxis after allogeneic stem cell transplantation?

Abstract  Cytomegalovirus (CMV) disease is a serious complication after allogeneic hematopoietic stem cell transplantation (HSCT) and is associated with high morbidity and mortality. Early detection of the disease by antigenemia testing and polymerase chain reaction (PCR) along with pre-emptive antiviral therapy has been shown to be very effective in decreasing the incidence of CMV. We performed an uncontrolled observational study in 21 patients after HSCT (14 related, 7 unrelated donors) to evaluate the efficacy and toxicity of foscarnet administered as prophylaxis for CMV reactivation. Ten patients received bone marrow, and eleven patients received peripheral blood stem cells. All patients received foscarnet prophylaxis to study side effects, incidence of CMV reactivation, CMV disease, and transplant-related mortality. Foscarnet (90 mg/kg) was given every 12 h, day +11 to day +16. Thereafter, foscarnet (90 mg/kg) was given once per day, three times per week until day +60. The incidence of CMV reactivation detected by antigenemia (pp65 antigen) or PCR was 23.8% (5 of 21 patients). Two patients developed CMV disease and one patient died of CMV-pneumonia. Seventeen patients (81%) reported severe side effects, such as gastrointestinal disturbance, headache, and urethritis. In eight patients (38%), the dose of foscarnet had to be reduced and, in six patients (28.5%), foscarnet application was discontinued because of side effects. Compared with other groups, we believe that the potential benefit of foscarnet administration in this early setting is outweighed by the risks of severe toxicity.

Key words  CMV · Prophylaxis · Foscarnet · Allogeneic stem cell transplantation

Introduction  Despite recent improvements in diagnosis and therapy, cytomegalovirus (CMV) disease after bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) is still associated with high morbidity and mortality [14, 15]. Acute graft versus host disease (GVHD), human leukocyte antigen (HLA) mismatching, unrelated transplantation, and T-cell depletion increase the risk of CMV reactivation [2, 15]. New strategies in the management of CMV infection include the measurement of pp65 antigen and the utilization of the polymerase chain reaction (PCR) to detect CMV antigenemia before the occurrence of CMV disease [5, 6, 17, 21, 23]. High-dose acyclovir prophylaxis after hematopoietic stem cell transplantation (HSCT) was another important improvement, which decreased the incidence of CMV infection and disease. In several randomized trials, high-dose acyclovir could reduce the incidence of CMV disease from 38% to 22% [2, 12, 16, 19, 20]. By detecting CMV antigenemia, many transplant centers introduced a pre-emptive therapy with ganciclovir or foscarnet. These antiviral drugs, however, show side effects, including bone marrow toxicity, renal dysfunction, and serum electrolyte disturbances [3, 21, 22].

In addition, it was demonstrated that ganciclovir prophylaxis did not improve transplant-related mortality because of hematotoxicity during engraftment [7, 10, 24]. There are only a few studies evaluating the efficacy of foscarnet prophylaxis after allogeneic HSCT. A study published by Bacigalupo and colleagues suggested that foscarnet prophylaxis may be helpful in reducing and delaying the risk of CMV infection and disease [3]. The study encouraged us to verify this modali-
ty and to evaluate the side effects of foscarnet in this early setting after BMT.

Patients and methods

Patients

Twenty-one recipients of related or unrelated HSCT were included in the open, nonrandomized study. The study had been approved by the local ethics board, and informed consent was obtained from all patients. In each case, the patient or the respective donor was CMV seropositive. Patients younger than 18 years or older than 60 years or with creatinine serum levels greater than 1.6 mg/dl were excluded. The median age was 35 years (range 19–53 years), 11 patients were male, and 10 patients were female. The patient characteristics are shown in Table 1.

Transplantation

Thirteen patients with related HLA-matched donors were treated with busulfan [3.1 mg/kg body weight (BW) i.v.; day –7 to day –4] and cyclophosphamide (50 mg/kg BW i.v.; day –3 to day –2) as per protocol. Nine patients received unmanipulated peripheral blood stem cells and four received unmanipulated bone marrow. Seven patients with unrelated donor and one patient with a related antigen-mismatched graft were treated with busulfan [3.1 mg/kg BW i.v.; day –9 to day –6], cyclophosphamide (50 mg/kg BW; day –5 to day –2), and antithrombocyte globulin (ATG, 3.1 mg/kg BW i.v.; day 1). Two patients were transplanted with CD34⁺-selected peripheral blood stem cells, and three patients were transplanted with unmanipulated bone marrow. In all patients, the infused counts of CD34⁺ cells were 4.4×10⁹/kg BW (range 0.7–9.6×10⁹/kg BW).

Immunosuppression

All patients, except for the five receiving CD34⁺-selected cells, received cyclosporin A and methotrexate for GVHD prophylaxis. The five patients receiving CD34⁺-selected cells were only administered cyclosporin A.

Infection and prophylaxis

All patients received antibiotic and antifungal prophylaxis with ciprofloxacin (1000 mg/day) and fluconazole (200 mg/day). All patients with allogeneic BMT/PBSCT received CMV prophylaxis according to the protocol used by Bacigalupo et al. [3]. During the high-dose chemotherapy, until day 10 after transplantation, acyclovir (500 mg/m²) was administered three times per day. From day 11 to day 16, patients received foscarnet sodium 90 mg/kg every 12 h (Foscavir, Astra GmbH, Wedel, Germany). All patients were hydrated with 1500 ml during application of foscarnet. The creatinine and the electrolytes were monitored daily. From day 17 to day 60, the patients were treated with foscarnet 90 mg/kg/day three times per week. All patients received high-dose immune globulin (intravenous immune globulin, Octagam) weekly. The foscarnet dosage was adjusted according to the creatinine serum levels. At first detection of CMV, reactivation therapy with foscarnet was interrupted, and patients were switched to ganciclovir (2×5 mg/kg/day). All patients received filtered leukocyte-free red blood products.

CMV monitoring

The PCR technique and pp65 CMV antigen detection were performed from ethylene diamine tetraacetic acid (EDTA)-treated blood samples, urine, and sputum once per week until day +120. The CMV-PCR technique was managed using a nonradioactive PCR-enzyme-linked immunosorbent assay [1]. The detection of the lower matrix protein pp65 antigen was performed using the alkaline phosphatase antialkaline phosphatase (APAAP) method concerning the immunochemical staining of Clonab CMV-labeled cytoxin preparations and tissue samples [4, 13].

Definitions of CMV reactivation (infection) and disease

CMV reactivation was diagnosed when a pp65 antigen was detectable or a PCR signal was positive in two consecutive tests. CMV disease was defined according to the Fourth International CMV Conference criteria [10].

Results

Side effects and toxicity of foscarnet

All patients were monitored for foscarnet-associated symptoms. During the first 10 days of foscarnet administration, 16 of 21 patients (76.2%) complained of gastrointestinal symptoms including nausea and vomiting. Five of these patients reported grade-III side effects according to the World Health Organization (WHO) grading system. Five patients complained of paresthesia, but none of these symptoms were graded as severe. Three patients reported symptoms of mild urethritis. One patient developed foscarnet-associated severe diabetes insipidus (DI) with an increasing urine volume up to 11.5 l/day. The diagnosis was confirmed by extremely high values of antidiuretic hormone (ADH) levels in serum (maximum 40.2 ng/l, day +12 post-transplant). After the discontinuation of foscarnet, symptoms of DI completely resolved. No seizures were seen during ap-

| Table 1 Patient characteristics. AML: acute myeloid leukemia; CML: chronic myeloid leukemia; ALL: acute lymphocytic leukemia; PNH: paroxysmal nocturnal hemoglobinuria; HLA: human leukocyte antigen; GVHD: graft versus host disease; CMV: cytomegalovirus |
|-----------------|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Donor type      | Diagnoses        | Acute GVHD      | Disease (CMV-pneumonia) | Death by CMV infection |
| Related, HLA matched | 13               | 3               | 2               | 1               |
| Related, HLA mismatched | 1           | 5               | 1               | 7               |
| Unrelated, HLA matched | 7           | 5               | 2               | 1               |
| Median age and range (years) | 35 (19–53)   | Gender | 11 Male/10 Female |

The five patients receiving CD34⁺-selected cells were only administered cyclosporin A.