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Donor and Recipient CMV Serostatus and Outcome of Pediatric Allogeneic HSCT for Acute Leukemia in the Era of CMV-Preemptive Therapy

Carolyn E. Behrendt,[1] Joseph Rosenthal,[2,3] Ellen Bolotin,[2,3] Ryotaro Nakamura,[2] John Zaia,[4] Stephen J. Forman[2]

In the era of cytomegalovirus (CMV)-preemptive therapy, it is unclear whether CMV serostatus of donor or recipient affects outcome of allogeneic hematopoietic stem cell transplantation (HSCT) among children with leukemia. To investigate, consecutive patients aged 0-18 who underwent primary HSCT for acute leukemia in 1997-2007 (HLA-matched sibling or unrelated donor, myeloablative conditioning, unmanipulated bone marrow or peripheral blood, preemptive therapy, no CMV prophylaxis) were followed retrospectively through January 2008. Treatment failure (relapse or death) was analyzed using survival-based proportional hazards regression. Competing risks (relapse and nonrelapse mortality, NRM) were analyzed using generalized linear models of cumulative incidence-based proportional hazards. Excluding 4 (2.8%) patients lacking serostatus of donor or recipient, there were 140 subjects, of whom 50 relapsed and 24 died in remission. Pretransplant CMV seroprevalence was 55.7% in recipients, 57.1% in donors. Thirty-five (25.0%) grafts were from seronegative donor to seronegative recipient (D−/R−). On univariate analysis, D−/R− grafts were associated with shorter relapse-free survival (RFS) than other grafts (median 1.06 versus 3.15 years, $P < .05$). Adjusted for donor type, diagnosis, disease stage, recipient and donor age, female-to-male graft, graft source, and year, D−/R− graft was associated with relapse (hazards ratio 3.15, 95% confidence interval 1.46-6.76) and treatment failure (2.45, 1.46-4.12) but not significantly with NRM (2.00, 0.44-9.09). In the current era, children who undergo allogeneic HSCT for acute leukemia have reduced risk of relapse and superior RFS when recipient and/or donor is CMV-seropositive before transplantation. However, no net improvement in RFS would be gained from substituting seropositive unrelated for seronegative sibling donors.

Biol Blood Marrow Transplant 15: 54-60 (2009)

KEY WORDS: Pediatric, Acute leukemia, Hematopoietic stem cell transplantation, Cytomegalovirus, Prognosis

INTRODUCTION

In the current era of effective prophylactic and preemptive therapy, cytomegalovirus (CMV), once a leading infectious cause of death after hematopoietic stem cell transplantation (HSCT), is now an infrequent cause of early mortality. Yet donor or recipient CMV seropositivity may still confer a survival disadvantage, particularly when the graft is T cell depleted [1]. Mechanisms proposed for an indirect adverse effect of CMV include virally mediated immunosuppression (resulting in increased risk of bacterial and fungal infections) [2,3] and increased risk of acute graft-versus-host disease (GVHD) [4,5].

In order to prevent CMV transmission from seropositive donor to seronegative recipient, it has been recommended that CMV-seronegative patients receive grafts from seronegative donors whenever possible [6]. For a seropositive recipient, on the other hand, the choice of donor is currently controversial [1,6,7]. Some studies have reported a beneficial effect of seropositive donor, either reduction in relapse [8,9] or reduction in nonrelapse mortality (NRM) [10,11], whereas other studies have found no benefit from seropositive donor [1,2,12,13].

Three pediatric studies have investigated the effect of donor and recipient CMV serostatus on HSCT outcomes. In the first 2 studies (one of Philadelphia chromosome-positive chronic myeloid leukemia [14], the other of acute or chronic leukemia [15]),

From the [1]Division of Biostatistics and Epidemiology; [2]Hematology and Hematopoietic Cell Transplantation; [3]Pediatrics; and [4]Virology, City of Hope National Medical Center and Beckman Research Institute, Duarte, California.

Financial disclosure: See Acknowledgments on page 59.

Correspondence and reprint requests: Carolyn E. Behrendt, PhD, City of Hope, 1500 E. Duarte Road, Duarte, CA 91010 (e-mail: cbehrendt@coh.org).

Received September 11, 2008; accepted October 23, 2008
1083-8791/09/151-0001$36.00/0
doi:10.1016/j.bbmt.2008.10.023

preemptive antiviral chemotherapy was not routinely used until the final years of study enrollment. No association was detected between relapse or NRM and donor or recipient serostatus [14] or seronegative donor-recipient pair [15]. In the third study, preemptive antiviral therapy was routine [16]. However, CMV prophylaxis was also standard; in addition, the sample was small and combined nonmalignant with malignant cases. In that study, the primary endpoint was CMV disease within 12 months after HSCT, but a possible association was noted ($P = .05$) between recipient CMV seropositivity and increased NRM.

Thus, for pediatric leukemia patients in the current era of preemptive therapy, it remains unclear whether CMV serostatus of donor and/or recipient affects the outcome of allogeneic HSCT. To investigate this question, we undertook a retrospective study among children with acute leukemia who underwent primary allogeneic HSCT with routine use of CMV-preemptive therapy.

METHODS

Sample

Consecutive patients aged 0-18 who underwent primary, myeloablative, allogeneic HSCT were studied retrospectively with the approval of the medical center's institutional review board. Eligible diagnoses were acute lymphocytic leukemia (ALL), acute myeloid or promyelocytic leukemia (AML), and myelodysplastic syndrome (MDS). Eligible donors were HLA-matched sibling (nonsyngeneic) or unrelated individuals. Eligible grafts were unmanipulated bone marrow or peripheral blood. Transplantations were performed between inception of the pediatric HSCT program in March 1997 and October 2007, and subjects were followed to relapse, NRM, or last contact through January 2008.

Surveillance for Early CMV Infection

Early CMV infection refers to viremia or disease with onset by day 100. Peripheral blood samples for CMV culture or polymerase chain reaction (PCR) were obtained twice weekly from day 21 through day 100. Specimens other than blood were obtained when clinically indicated. CMV viremia was defined as 1 positive culture, 2 consecutive positive PCR tests, or 1 quantitative PCR with viral load $\geq$5000/mL (or $\geq$1000/mL during high-dose corticosteroid therapy for acute GVHD [aGVHD]). Per published guidelines [17], CMV disease was defined as clinical symptoms together with detection of CMV in fluid, lavage, or biopsy specimen from the affected organ, except CMV retinitis, which was diagnosed on retinal examination by an experienced ophthalmologist.

CMV-Preemptive Therapy

Preemptive therapy consisted of a week of induction therapy using either ganciclovir (5 mg/kg i.v. twice daily) or valganciclovir (450 mg/m^2 orally twice daily), followed by 5 weeks of maintenance therapy with these same drugs given once daily, 5 days per week; foscarnet was used instead in 1 patient. CMV prophylaxis was not used. Standard HSCT procedures included acyclovir (pediatric dose 250 mg/m^2 i.v. every 12 hours) from day -1 to day $+25$ as prophylaxis against varicella zoster and herpes simplex viruses.

Definitions

Disease stage was defined as early (AML and ALL in first complete remission and MDS subtype refractory anemia), intermediate (AML or ALL in second or subsequent complete remission or in first relapse), or advanced (AML or ALL in second or higher relapse or primary induction failure, MDS subtype refractory anemia with excess blasts or in transformation, or MDS, not otherwise classified). Acute GVHD refers to cases that were grade 2-4 per Keystone Consensus Criteria [18].

Statistical Analysis

Patients who did not achieve remission after transplantation were considered to have relapsed on day 1. No relapse or NRM was observed after 4 years from HSCT, by which milestone fewer than 20% of subjects remained in the cohort. Therefore, 4 years was the follow-up period chosen for study. Relapse-free survival was estimated using the Kaplan-Meier method [19]. Treatment failure (relapse or NRM) was analyzed using Cox proportional hazards regression [20].

Relapse and NRM constitute competing types of treatment failure: the occurrence of 1 type precludes the occurrence of the other. Cumulative incidence of competing risks was calculated and compared between groups as described by Gray [21]. In the presence of competing risks, the common practice in cancer studies of censoring 1 type of failure in order to model the other has been criticized as logically flawed [22]. Therefore, relapse and NRM were modeled using a methodology appropriate for competing risks: generalized linear models (complementary log-log link function, PROC GENMOD in SAS Version 9.1, SAS Institute Inc., Cary, NC) of cumulative incidence-based proportional hazards were constructed using the pseudovalues approach of Klein and Andersen [23,24]. As in [24], a grid of 5 time points was used when calculating pseudovalues. Specifically, days 50, 90, 160, 240, and 540 demarcated approximately equal numbers of treatment failures per time period. The proportionality of hazards over time was verified [24]. If a hazard was time dependent, a cutpoint was chosen among the 5 grid time points. A similar