Leukemia Research 57 (2017) 37–44

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Cytomegalovirus reactivation is associated with a lower rate of early relapse in myeloid malignancies independent of in-vivo T cell depletion strategy

Talal Hilal[a,b,*], Stacey Slone[d], Shawn Peterson[a], Charles Bodine[a], Zartash Gul[c,e]

[a] Department of Internal Medicine, University of Kentucky, Lexington, KY, United States
[b] Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, AZ, United States
[c] Division of Hematology and Blood and Marrow Transplant, University of Kentucky Markey Cancer Center, Lexington, KY, United States
[d] Biostatistics Shared Resource Facility, University of Kentucky Markey Cancer Center, Lexington, KY, United States
[e] Division of Hematology, University of Cincinnati Cancer Center, Cincinnati, OH, United States

ARTICLE INFO

Article history:
Received 27 November 2016
Received in revised form 22 February 2017
Accepted 26 February 2017
Available online 1 March 2017

Keywords:
Cytomegalovirus
CMV reactivation
Leukemia
Allogeneic HSCT
Stem cell transplant
T-cell depletion

ABSTRACT

The association between cytomegalovirus (CMV) reactivation and relapse risk has not been evaluated in relation to T cell depletion strategies. We evaluated 93 patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) and analyzed the association between T cell depletion strategies with the cumulative incidence of relapse and CMV reactivation. A total of 33% of patients who received ATG vs. 34% who received alemtuzumab developed CMV reactivation. The cumulative incidence of relapse was 3% at 1 year and 20% at 3 years in patients with CMV reactivation vs. 30% at 1 year and 38% at 3 years in patients without CMV reactivation ($p = 0.02$). When analyzed separately, this effect persisted in the myeloid, but not the lymphoid group. There was a numerical trend towards increased non-relapse mortality (NRM) in patients with CMV reactivation, especially in the myeloid group. The choice of T cell depleting agent and the rate of CMV reactivation were not associated with different overall survival (OS) rates. These results suggest that the choice of T cell depletion strategy may have similar effects on rates of CMV reactivation, disease relapse, and survival. Further studies examining these variables in patients not exposed to in-vivo T cell depleting agents may be of interest.

1. Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus that is responsible for significant morbidity and mortality in immunocompromised patients. The incidence of CMV reactivation is increased in patients with allogeneic hematopoietic stem cell transplant (HSCT) due to conditioning regimens that suppress the immune system. Early detection of reactivation allows for the use of preemptive therapy which has reduced complications associated with CMV disease.

Several studies have reported that early CMV reactivation in the post allogeneic-HSCT has been shown to reduce leukemic relapse in adult patients with acute myeloid leukemia (AML) [1,2]. However, later studies suggested increased non-relapse mortality (NRM) and no difference in overall survival (OS) between cohorts [3]. Furthermore, CMV reactivation may be influenced by the conditioning regimen as shown in one study that reported a protective effect restricted to patients who received myeloablative conditioning (MAC) [4].

More recently, it has been found that the use of anti-thymocyte globulin (ATG) may negate the antileukemic effects of CMV reactivation in patients with AML [5]. We sought to compare the incidence of CMV reactivation, disease relapse and survival outcomes in two cohorts of patients who received either alemtuzumab or ATG as part of their conditioning regimen for in-vivo T cell depletion.

2. Methods

2.1. Study design and eligibility

This is a retrospective, single-institution, observational study that included 93 patients who underwent allogeneic HSCT between January 2010 and January 2015 for a hematologic malignancy. The patient population was then divided into two groups; one that

* Corresponding author at: 5777 E. Mayo Boulevard Phoenix, AZ 85054, United States.
E-mail address: hilal.talal@mayo.edu (T. Hilal).

http://dx.doi.org/10.1016/j.leukres.2017.02.009
0145-2126/

received alemtuzumab (41%) and one that received ATG (59%) for in vivo T cell depletion as part of graft versus host disease (GVHD) prophylaxis. The study was approved by the University of Kentucky institutional review board.

The eligibility criteria included adults greater than 18 years of age with a hematologic malignancy who received either alemtuzumab or ATG as part of their conditioning regimen for GVHD prophylaxis. Patients were excluded if they underwent cord blood transplant, if they were HIV positive, or if they received T cell depleting agents for a reason other than transplant.

2.2. Conditioning regimens and supportive care

A total of 45 patients (48%) received MAC regimens consisting of IV busulphan (BU) combined with either high-dose cyclophosphamide (Cy) or fludarabine (FLU); or high-dose Cy with 12.0 Gy TBI. A total of 48 patients (52%) received reduced-intensity conditioning (RIC) conditioning regimens consisting of IV FLU combined with melphalan, or IV FLU combined with low-dose BU.

Transfusion support using leukocyte-filtered blood products was provided to maintain a hemoglobin > or equal to 8 g/dL and to prevent severe thrombocytopenia (< or equal to $20 \times 10\hat{9}$/L). Antimicrobial prophylaxis was administered to all patients along with acyclovir for 1 year. IgG levels were monitored and patients were given IVIG preemptively if IgG levels were <400 mg/dL.

2.3. GVHD prophylaxis

Prophylaxis of GVHD consisted of tacrolimus and a short-course of methotrexate in all patients. In addition, alemtuzumab was administered to 38 patients (41%) at a dose of 20 mg daily over 3–5 days (on days −7, −6, −5, −4, −3), and ATG was administered to 55 patients (59%) at a dose of 5 mg/kg over two or three days (on days, −4, −3, −2, or −3, −2).

2.4. Definitions

Monitoring for CMV infection/reactivation was done using PCR testing methods. In particular, for specimens tested from 2010 to April 2013, whole blood specimens were used; any value >200 copies/mL, or <200 copies/ml with a 2-fold rise in 1-week follow-up was considered as CMV reactivation. Since April 2013, plasma specimens were used; any value >137 copies/mL was defined as CMV reactivation. A result that is reported as positive but without a measurable CMV titer was not considered reactivation unless a titer became measurable on repeat testing.

Morphologic relapse of the leukemia was the primary outcome of patients transplanted in complete remission (CR) and progression of disease for patients who received grafts with active disease. Marrow examination was performed after HSCT at 100 days, and at 12 months thereafter if not otherwise indicated. Donor chimerism was checked at day 30, 60, 100, 180 and 1 year after transplant if not otherwise indicated.

Disease etiology was defined as primary for all de novo cases of myeloid or lymphoid malignancies, and secondary for cases that developed from a previous clonal disorder of hematopoiesis or after exposure to a leukemogenic agent. The assessment and grading of acute GVHD was primarily based on clinical findings and followed the International Bone Marrow Transplant Registry (IBMTR) grading system. The assessment of chronic GVHD was primarily based on clinical findings. Diagnosis was confirmed histologically whenever indicated and clinically possible

2.5. CMV monitoring and pre-emptive therapy

CMV reactivation was routinely monitored twice weekly during the inpatient post-transplantation course and weekly in the outpatient setting. CMV reactivation was pre-emptively treated with either IV ganciclovir or oral valganciclovir. Foscarnet was substituted in case of cytopenias. Antiviral induction therapy was continued for 14 days followed by maintenance treatment for 14 days or until two consecutive negative surveillance results were recorded.

2.6. Clinical endpoints and statistical analysis

The primary end point included the cumulative incidence of relapse and the breakdown between alemtuzumab and ATG in patients with CMV reactivation. The secondary ones were the cumulative incidence of NRM and OS in relation to CMV reactivation and the T cell depletion agent.

The median follow-up for OS from transplantation was 11.7 months (range; 0.4–61.4 months). The cumulative incidences of relapse and NRM were estimated by the cumulative incidence function, comparing the curves of the main event (relapse), in the presence of a competing event (death without previous relapse) by the Gray test. Similarly, CMV reactivation was estimated using both relapse and death without previous CMV reactivation as competing events. The univariate analyses were performed for the following prognostic factors: recipient age (>50 vs. 50 years), gender, HLA mismatch (8/10, 9/10 vs. 10/10), conditioning regimen (myeloablative vs. RIC), disease status at transplantation (less than CR vs. CR2/3 vs. CR1), serostatus, donor and recipient pre-transplantation CMV status (positive vs. negative), occurrence of acute GVHD Grade A-D and/or chronic GVHD (any vs. none), malignancy (myeloid vs lymphoid), transplant year and diagnosis. Multivariate Fine and Gray competing risk regression models were ran for risk of relapse and non-relapse mortality including covariates that demonstrated significance in the univariate models: disease etiology and acute GVHD (NRM only) in addition to CMV reactivation and T-cell depletion.

The OS curve was estimated by the Kaplan–Meier method, comparing the two arms by the log-rank test. Patient characteristics were tested using the Wilcoxon rank sum and Fisher's exact test, as appropriate. All reported P-values were two-sided, at the conventional 5% significance level. Data were analyzed using SAS 9.4.

3. Results

3.1. Patient characteristics

Patient and transplant characteristics of the two cohorts who received ATG or alemtuzumab are summarized in Table 1. Patients who received ATG or alemtuzumab were similar relative to age, sex, HLA matching, preparative regimen, and onset of acute GVHD. While patients in the alemtuzumab group were less likely to be transplanted with active disease, the difference was not statistically significant.

3.2. CMV reactivation and T-cell depletion strategy

A total of 31 patients (33%) had CMV reactivation resulting in a cumulative incidence of CMV reactivation of 29.0% at 12 months with 87% of the CMV reactivations occurring within the first 100 days post HSCT. A total of 18 patients (33%) who received ATG had CMV reactivation, and 13 patients (34%) who received alemtuzumab. At 1 year, 34% of alemtuzumab patients had experienced CMV reactivation compared to 33% of ATG patients ($p = 0.87$). The cumulative incidence of CMV reactivation was 21% of lymphoid