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Favorable Outcomes in Patients with High Donor-Derived T Cell Count after In Vivo T Cell–Depleted Reduced-Intensity Allogeneic Stem Cell Transplantation

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Patients with hematologic malignancies were conditioned using a rabbit antithymocyte globulin–based reduced-intensity conditioning regimen for allogeneic stem cell transplantation. Donor-derived $CD3^+$ cell count (ddCD3), a product of $CD3^+$ cell chimerism and absolute $CD3^+$ cell count, when $<110/\mu L$ at 8 weeks post-stem cell transplantation predicted a high risk of sustained mixed chimerism and relapse. Alternatively, patients with a higher ddCD3 developed graft-versus-host disease more frequently, and when partially chimeric, had higher rates of conversion to full donor chimerism after withdrawal of immunosuppression. Early data from our small cohort of patients indicate that ddCD3 at 8 weeks may be used to guide decisions regarding withdrawal of immunosuppression and administration of donor lymphocyte infusion in partially T cell–depleted reduced-intensity regimens.

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INTRODUCTION

Reduced-intensity conditioning regimens for allogeneic stem cell transplantation (SCT) are well tolerated but are characterized by variable immunologic recovery, particularly when T cell depletion (TCD) is performed to reduce graft-versus-host disease (GVHD) risk [1-5]. TCD may be performed either in vivo by administration of antithymocyte globulin (ATG) during conditioning or ex vivo by various allograft T cell–purging techniques. ATG reduces the risk of chronic GVHD and nonrelapse mortality in matched related donor (MRD) SCT recipients conditioned with a myeloablative regimen [6]. In addition, outcomes in unrelated donor (URD) SCT are improved when ATG is incorporated in the conditioning regimen [7,8] or when the allograft is ex vivo T cell–depleted with CD6 monoclonal antibodies [9].

However, when TCD is performed in SCT with a reduced-intensity conditioning regimen, post-SCT outcomes such as GVHD and relapse are influenced by the level of donor T cell chimerism achieved. Mixed donor–recipient chimerism in T cells often complicates such transplantations. A recent study found that the use of CD52 monoclonal antibody for TCD along with a reduced-intensity regimen resulted in a 50% incidence of mixed chimerism (MC) in T cells at day 100 post-SCT and that declining T cell chimerism was associated with increased risk of relapse [10]. Other studies have reported similarly poor outcomes with MC in the T cells in the first month after reduced-intensity SCT, particularly when T cell chimerism was <60% [11].

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The level of T cell chimerism after SCT also affects the response to donor lymphocyte infusion (DLI). In one study, patients conditioned with ATG and a reduced-intensity regimen before allografting had a high rate of graft loss despite prophylactic DLI if T cell chimerism was <20% donor and a high rate of conversion to full donor chimerism (FC) if T cell chimerism was >40% donor [12]. In addition to T cells, natural killer (NK) cell chimerism also has been reported to affect the risk for GVHD and graft loss in patients undergoing T cell–replete nonmyeloablative allogeneic SCT [13], highlighting the interactions among various effectors of cellular immunity. In general, studies incorporating T cell–replete allografts have reported frequent mixed donor–recipient chimerism in T cells early after reduced-intensity SCT, which over time converts to FC as immunosuppression is withdrawn. Often this shift in chimerism is accompanied by the development of GVHD, potentially compromising outcome. Conversely, in patients undergoing TCD allogeneic SCT, withdrawal of immunosuppression results in less precisely predictable outcomes in patients with mixed T cell chimerism, with either maintenance of stable MC or occasionally graft loss observed. MC is accompanied by an increased risk of relapse [14,15]. DLI may be used to convert patients with MC to FC and reduce the risk of relapse, but it is complicated by the development of acute or chronic GVHD in as many as 50% of patients [16,17], even when CD8-depleted DLI is used [18,19]. Alternative strategies in patients with MC, such as administration of low-dose prophylactic DLI, although less likely to cause GVHD, are ineffective [4].

Given the unfavorable outcomes associated with the mixed chimeric state, a reliable predictor for the expected evolution of mixed T cell chimerism is needed to help guide clinical decision making regarding withdrawal of immunosuppression and DLI. An alternative immune recovery parameter with prognostic value is T cell recovery posttransplantation [20,21]. We decided to combine this measure with T cell chimerism and to examine the predictive value of a calculated donor-derived T cell count for clinical outcomes after allogeneic SCT conditioned with rabbit ATG and reduced-intensity total body irradiation (TBI). This regimen is based on preclinical studies in murine transplantation demonstrating engraftment across the major histocompatibility complex barrier when T cell antibodies were combined with low-dose irradiation [22,23]. The feasibility of this approach in human transplantation has been demonstrated in clinical trials, which established a low risk of severe acute GVHD, albeit with high rates of mixed donor–recipient chimerism and occasional graft loss [1,3,12,24]. The present trial examined the effect of two doses of rabbit ATG in recipients of allogeneic SCT, with posttransplantation immune reconstitution as the trial's primary endpoint (Clinicaltrials.gov identifier: NCT00709592).

PATIENTS AND METHODS

Patients and Eligibility

Consecutive patients were enrolled on a prospective randomized phase II clinical trial, approved by the Institutional Review Board at Virginia Commonwealth University. To be eligible, patients had to be between 18 and 70 years of age, have a recurrent or high-risk hematologic malignancy, and have adequate end-organ function and performance status. Patients aged <50 years had to be ineligible for conventional myeloablative conditioning because of comorbidity. Each patient was required to have a 7/8 or 8/8 locus-matched related donor (MRD) or unrelated donor (URD), with high-resolution typing performed for HLA-A, -B, -C, and -DRB1.

ATG + TBI Conditioning Regimens

The patients were randomized between two different doses of rabbit ATG (Thymoglobulin; Genzyme, Cambridge, MA), 2.5 or 1.7 mg/kg adjusted ideal body weight/day, given i.v. on days -9 through -7, followed by TBI to a total dose of 4.5 Gy, delivered in three 1.5-Gy fractions, with two doses on day -1 and the final dose on day 0. Methylprednisolone 2 mg/kg was given as premedication for ATG. GVHD prophylaxis was tacrolimus given orally starting on day -2 with tapering starting at approximately 12 weeks posttransplantation. Mycophenolate mofetil was given orally at a dose of 15 mg/kg twice daily from day 0 to day 28. Granulocyte colony-stimulating factor (G-CSF) was given at a dose of 5 μg/kg/day from day 4 until myeloid engraftment occurred. Blood stem cells were collected using G-CSF 10 μg/kg/day s.c. on days 1-5. Escalating-dose DLI was permitted beyond 8 weeks post-SCT for the management of declining or persistent MC (initial dose, 1×10^6 $CD3^+$ cells/kg) and for disease progression (initial dose, 5×10^6 $CD3^+$ cells/kg).

T Cell Engraftment Analysis

Donor engraftment was assessed by chimerism analyses performed at 4, 8, 12, and 24 weeks after SCT on whole-blood, granulocytes, and total T cells. Blood cell separation was done using immunomagnetic beads (Miltenyi Biotec, Auburn, CA) enriched for CD15- and CD3-expressing cells in a Miltenyi Biotech AutoMACS Pro Separator. DNA was isolated using a Qiagen EZ1 200-μL Whole-blood Isolation Kit (Qiagen, Valencia, CA) on a Qiagen EZ1 Biorobot. Polymerase chain reaction was performed with the