CLINICAL RESEARCH

Rituximab Administration within 6 Months of T Cell-Depleted Allogeneic SCT is Associated with Prolonged Life-Threatening Cytopenias

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The monoclonal anti-CD20 antibody Rituximab (RTX) is increasingly used in allogeneic stem cell transplantation (SCT) to treat lymphoproliferative disorders and chronic graft-versus-host disease (GVHD). RTX administration can be complicated by delayed and prolonged neutropenia, but the mechanism is unclear. We report the occurrence of profound cytopenias following RTX given in the conditioning regimen or early after T cell-deplete SCT to treat B cell lymphoproliferative disorders or chronic GVHD (cGVHD). Between 2006 and 2009, 102 patients (median age: 43 years, range: 13-68 years), received a myeloablative matched-sibling T cell-deplete SCT for lymphoid or myeloid hematologic disorders. Neutropenia occurring within 4 weeks of treatment developed in 16 of 17 patients given RTX within the first 190 days after SCT. Fourteen patients developed severe neutropenia (count <0.5 K/μL) lasting up to 10 months and 12 required hospitalization to treat severe neutropenic infections. Six of the 14 patients died of infection complicating GVHD treatment. Recovery of lymphocytes and immunoglobulins was also delayed, with a significantly lower absolute lymphocyte counts (ALC) at 9 months and 12 months post-SCT compared to patients with cGVHD not treated with early RTX ($P < .02$). In contrast, patients receiving RTX 1 year after SCT experienced only moderate neutropenia 3 to 5 months after treatment lasting 10 to 20 days while maintaining absolute neutrophil count (ANC) $>1.0 \times 10^9$/L. Although RTX rapidly controlled cGVHD, we conclude that its administration early after T cell-deplete SCT is associated with prolonged profound and life-threatening cytopenias, and should be avoided.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (SCT) offers the possibility of a curative treatment for malignant and nonmalignant hematologic diseases. However, SCT is frequently complicated by graft-versus-host disease (GVHD), which remains a major cause of transplant-related morbidity and mortality (TRM). The anti-CD20 chimeric monoclonal antibody Rituximab (RTX) given prior to, or during, conditioning for T cell-replete SCT has been reported to decrease acute GVHD, and chronic GVHD (aGVHD, cGVHD), and may decrease TRM [1–3]. Because of these promising results, RTX has been increasingly used to treat cGVHD [4].

RTX induces response rates in about two-thirds of patients with cGVHD. Response varies by organ, with an estimated response rate of 60% for cGVHD of the skin compared to approximately 30% for cGVHD of the gastrointestinal (GI) tract, liver, or lung [5]. Apart from acute infusion reactions, RTX is well tolerated. However, late adverse effects are being identified with increased frequency. Late-onset neutropenia is estimated to occur in up to 35% of patients treated for B cell malignancies in the non-SCT setting [6]. Thrombocytopenia (platelets <75 K/μL) and anemia (hemoglobin <10 g/dL) have also been reported, with an incidence of approximately 12% and 6%, respectively [7].

Since 2006, we have used RTX in the early transplant period after myeloablative SCT, either as part of the conditioning regimen for B cell malignancies, or to treat emerging cGVHD. Although patients

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with cGVHD responded well to RTX, all patients who received RTX within 6 months after SCT had a high risk of developing severe cytopenias. Here, we describe the clinical outcome of RTX-treated patients and discuss the possible etiology of RTX-induced cytopenias in this patient population.

MATERIALS AND METHODS

Patients and Controls

Between February 2004 and April 2009, 102 consecutive patients underwent a T cell-depleted SCT from an HLA-identical sibling in 3 successive National Heart, Lung and Blood Institute (NHLBI) institutional review board-approved protocols (04-H-0112, 06-H-0248, and 07-H-0136). Patients and donors provided written informed consent before enrolling in the transplantation protocol.

All patients received a conditioning regimen of fludarabine 125 mg/m^2 over 5 days, fractionated total-body irradiation (TBI) 12 Gy (4.0 Gy if over 55y) in 8 fractions over 4 days, followed by cyclophosphamide 120 mg/kg over 2 days. All transplants were depleted of T lymphocytes with the Isolex system (protocol 04-H-0112), or with the Miltenyi CliniMacs system (Miltenyi Biotec Inc., Auburn, CA) (protocols 06-H-0248 and 07-H-0136) as previously described [8,9]. In protocols 04-H-0112, 06-H-0248 patients received an infusion of donor lymphocytes between days 60 to 90 after SCT. In protocol 07-H-0136 patients received 5×10^6 selectively depleted CD3$^+$ cells/kg on day 0, as previously described [10].

Only patients surviving 6 months or longer after SCT were included in the analysis to allow sufficient time for the development of cGVHD, and to exclude patients that experienced early deaths because of unrelated causes. Of the 95 patients surviving 6 months or longer after SCT, 17 received RTX within 6 months of SCT. Twenty-eight patients developed cGVHD but did not receive RTX early after SCT (4 received RTX 1-7 years after SCT), 18 of whom received an SCT prior to the use of RTX for treatment of cGVHD at our institution and were therefore considered the historic controls for this analysis. Fifty patients did not develop cGVHD and did not receive RTX at any time after SCT. Chronic GVHD was diagnosed and graded consistent with NIH consensus criteria [11].

GVHD Prophylaxis

All patients received low-dose (LD) cyclosporine (CsA) (target plasma level, 100-200 μg/mL), starting on day −4 and continuing according to protocol to day +21 or day 90 after SCT. CsA was reinitiated and continued for approximately 3 months after donor lymphocyte infusions (DLIs) given by protocol or to treat incipient rejection as documented by falling counts and falling donor T cell chimerism. CsA was continued or reinitiated if cGVHD developed, and patients were treated off protocol for cGVHD refractory to CsA and prednisone.

Infection Prophylaxis and Treatment

Standard prophylaxis against infection included fluconazole and bactrim given for at least 6 months after transplantation, and twice weekly surveillance for cytomegalovirus (CMV) DNA by polymerase chain reaction (PCR). Treatment of infections was in accordance with the Guidelines for Management in Allogeneic Hematopoietic Stem Cells Transplant Recipients published by the Center for Disease Control (CDC) (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm). Granulocyte colony stimulating factor (G-CSF) was administered in all cases to maintain and absolute neutrophil count (ANC) >500/μL.

RTX Administration and Response Criteria

RTX given in the first 6 months after SCT was administered by intravenous infusions of RTX (375 mg/m^2 per infusion) at 2 to 4 weekly intervals posttransplant to treat cGVHD (15 patients), Epstein-Barr virus (EBV) lymphoproliferative disease (1 patient), and autoimmune hemolytic anemia (1 patient). Three patients with B cell malignancies that received RTX for treatment of cGVHD also received RTX immediately prior to, or as part of, the SCT conditioning regimen. In addition, 4 patients received RTX 1 to 7 years post-SCT at the same dose and schedule to treat cGVHD. Response of cGVHD to RTX was assessed 1 month after the last infusion. Complete response (CR) was defined as resolution of all manifestations of cGVHD in involved organs. A partial response (PR) was defined as an improvement in 1 or more involved organ without any progression or new organ involvement. Resistance was defined as no response or worsening cGVHD requiring alternative therapy.

Statistical Analysis

Survival was measured to the last contact date or death. Univariate and multivariate analyses were performed using Cox proportional-hazard regression model, including all factors associated with a *P*-value <.2 by univariate analysis, and all factors statistically different among the early RTX and other groups (P <.10). A stepwise backward procedure was then used with a cutoff significance level of .05 to remove factors from the model. *P*-values are 2 sided, with a type I error rate fixed at .05. Statistical analyses were performed with SPSS 15.0 and Prism 4 software.