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Comparison of Subcutaneous versus Intravenous Alemtuzumab for Graft-versus-Host Disease Prophylaxis with Fludarabine/Melphalan–Based Conditioning in Matched Unrelated Donor Allogeneic Stem Cell Transplantation

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A B S T R A C T

The objective of this study was to compare infusion-related reactions and outcomes of using subcutaneous (subQ) alemtuzumab versus intravenous (i.v.) alemtuzumab as graft-versus-host disease (GVHD) prophylaxis for matched unrelated donor stem cell transplantations. Outcomes include incidence of cytomegalovirus (CMV)/Epstein-Barr (EBV) viremia, development of CMV disease or post-transplantation lymphoproliferative disorder, fatal infections, acute and chronic GVHD, time to engraftment, relapse rate, and survival. We conducted a retrospective study of all adult matched unrelated donor stem cell transplantations patients who received fludarabine/melphalan with subQ or i.v. alemtuzumab in combination with tacrolimus as part of their conditioning for unrelated donor transplantation at New York-Presbyterian/Weill Cornell Medical Center from January 1, 2012 to March 21, 2014. Alemtuzumab was administered at a total cumulative dose of 100 mg (divided over days −7 to −3). Forty-six patients received an unrelated donor stem cell transplantation with fludarabine/melphalan and either subQ (n = 26) or i.v. (n = 20) alemtuzumab in combination with tacrolimus. Within the evaluable population, 130 subQ and 100 i.v. alemtuzumab doses were administered. For the primary outcome, ≥grade 2 infusion-related reactions occurred in 11 (8%) versus 25 (25%) infusions in the subQ and i.v. cohorts, respectively ($P = .001$). Overall, 12 injections (9%) in the subQ arm versus 26 infusions (26%) in the i.v. arm experienced an infusion-related reaction of any grade ($P = .001$). There were no significant differences between the subQ and i.v. arms in rates of reactivation of CMV/EBV, development of CMV disease or post-transplantation lymphoproliferative disorder, fatal infections, acute and chronic GVHD, relapse, or survival. Subcutaneous administration of alemtuzumab for GVHD prophylaxis was associated with fewer infusion-related reactions compared with i.v. administration in the SCT setting. Incidences of acute and chronic GVHD were similar between both arms. There was also no difference in reactivation of CMV/EBV viremia, development of CMV disease or post-transplantation lymphoproliferative disorder, fatal infections, relapse, or survival.

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INTRODUCTION

Allogeneic stem cell transplantation is an important treatment option for various malignant and nonmalignant conditions. However, graft-versus-host disease (GVHD) remains a major cause of post-transplantation morbidity and mortality. Alemtuzumab is a humanized monoclonal antibody that targets the CD52 antigen, which is expressed on the surface of T and B lymphocytes, monocytes, eosinophils, macrophages, and some dendritic cells but not on hematopoietic progenitor cells [1]. Based on previously published data, alemtuzumab-containing regimens for allogeneic stem cell transplantation have shown substantial benefit in reducing acute and particularly chronic GVHD [1,2], with survival rates comparable to those after similar regimens with conventional GVHD prophylaxis [3,4].

Many centers, including our own, have adopted alemtuzumab as part of their standard transplantation GVHD prophylaxis [5]. However, intravenous (i.v.) administration of

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alemtuzumab is commonly accompanied by infusion-related side effects, ranging anywhere from local injection site reactions to anaphylaxis [6]. The subcutaneous (subQ) route of administration has been shown to reduce the incidence of infusion-related reactions without a decrease in efficacy when used for chronic lymphocytic leukemia, but its use has not been compared in adult stem cell transplantation [6,7]. In early 2012, we introduced the routine use of subQ alemtuzumab in our unrelated donor transplantation patients. The goal of the current study was to compare the side effect profile and efficacy of subQ versus i.v. alemtuzumab in unrelated donor stem cell transplantation.

Patients and Treatment

This was a institutional review board–approved retrospective cohort study conducted at New York-Presbyterian/Weill Cornell Medical Center and included all adult patients (≥18 years of age) undergoing unrelated donor transplantation using fludarabine-melphalan-alemtuzumab conditioning between January 1, 2012 and March 21, 2014.

Patients received fludarabine 30 mg/m^2/day i.v. on day −7 to day −3 and melphalan 140 mg/m^2/day on day −2. For GVHD prophylaxis, patients received alemtuzumab 20 mg/day i.v. over 4 hours or subQ for 5 consecutive days (days −7 to −3) and tacrolimus starting day −2, which was routinely continued until day +180 unless patients developed GVHD (Figure 1). The alemtuzumab subQ formulation was administered as undiluted drug, available as 30 mg/mL vials, for each dose. Tacrolimus target trough levels were maintained between 5 ng/mL and 15 ng/mL. In a few cases, tacrolimus was replaced by either mycophenolate mofetil or sirolimus because of patient intolerance. For patients who developed GVHD, immunosuppressants were adjusted, as clinically required.

Acetaminophen 650 mg and diphenhydramine 50 mg were given to prevent infusion-related reactions from alemtuzumab. Additionally, for the i.v. cohort, methylprednisolone 2 mg/kg was given before alemtuzumab followed by 1 mg/kg halfway through the infusion on each day of infusion. Patients in the subQ cohort received hydrocortisone 100 mg before alemtuzumab. Anti-infective prophylaxis included levofloxacin 500 mg daily until engraftment, fluconazole 400 mg daily or voriconazole 200 mg twice daily until the patient was off all immunosuppressive medications, and sulfamethoxazole/trimethoprim 1 double-strength tablet twice daily from admission through day −2. At day +30 after transplantation, patients resumed pneumocystis pneumonia prophylaxis. For pre-emptive cytomegalovirus (CMV) treatment, all CMV IgG sero-positive donor and/or recipient patients received ganciclovir (5 mg/kg i.v. twice daily from day of admission until day −2), then acyclovir (500 mg/m^2 if <60 years old or 250 mg/m^2 if ≥60 years old every 8 hours i.v. from day −1 until engraftment), followed by high-dose oral valacyclovir (2 g if <60 years old or 1 g if ≥60 years old 4 times daily until day +150) [8]. After day +150, patients received valacyclovir 500 mg orally twice daily, which continued for a minimum of 1 year after stem cell transplantation or longer if patients continued on immunosuppressive medications. All CMV-IgG seronegative (donor and recipient) patients received oral valacyclovir 500 mg twice daily starting on day −1, which continued for a minimum 1 year after stem cell transplantation or longer, if patients remained on immunosuppressive medications. Patients received filgrastim starting day +5 after transplantation or, in some cases, after day +10. Transfusion support was administered if indicated per institutional policy (packed red blood cells for hemoglobin <8 grams/dL and platelets if <10,000/μL).

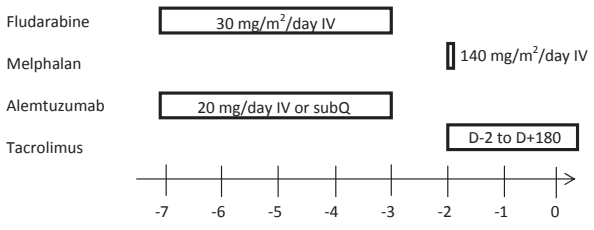

Figure 1. Treatment plan.

Outcomes and Definitions

The primary outcome was the incidence of ≥grade 2 infusion-related reactions within 24 hours of each subQ and i.v. alemtuzumab dose. *Infusion-related reactions* were defined as local injection site reactions (swelling/erythema), fever (defined as ≥38°C), chills/rigors, rash/urticaria, hypotension, bronchospasms/dyspnea, and anaphylaxis. The grade for each infusion-related reaction, as well as for hypotension, was determined using the Common Terminology Criteria for Adverse Events/Cancer Therapy Evaluation program criteria V4.0 (Table 1). Secondary outcomes included incidence of CMV viremia or disease, Epstein-Barr (EBV) viremia and post-transplantation lymphoproliferative disorder, fatal infections, relapse rate, and overall survival in the first year. Times to neutrophil and platelet engraftment and incidences of acute and chronic GVHD were also analyzed.

CMV viremia was defined as the first positive polymerase chain reaction (PCR) ≥200 copies/mL and *CMV disease* was defined as presence of CMV viremia with organ involvement (pneumonia, retinitis, colitis, or marrow involvement) up to 2 weeks after initiation of treatment. *Recurrence* of CMV viremia was defined as CMV viremia occurring after 2 consecutive negative real time PCR assays after treatment of initial episode of infection and requiring empiric treatment. EBV viremia was also recorded at the first positive PCR (≥200 copies/mL) and diagnosis of post-transplantation lymphoproliferative disorder was based on positron emission tomography scan or tissue biopsy. *Neutrophil engraftment* was defined as the first of 3consecutive days with an absolute neutrophil count ≥ .5 × 10^9/L. *Platelet engraftment* was defined as the first of 3 consecutive days with a platelet count ≥ 20 × 10^9/L that was maintained without transfusion support for 7 consecutive days. Acute GVHD assessment and grading were based on the consensus conference on acute GVHD grading [9]. Assessment and grading of chronic GVHD was based on the National Institutes of Health consensus development project on criteria for clinical trials in chronic GVHD [10].

Statistical Analysis

Fisher's exact or the chi-square test were used to compare categorical variables between groups. Mann-Whitney test was used to compare continuous variables. Group comparisons were 2-sided with a type 1 error of <.05. Estimates for each group are reported along with 95% confidence intervals. Breslow-Gehan-Wilcoxon tests were used to compare the time-related measures between groups.