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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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Abstract
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
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/m²/day i.v. on day −7 to day −3 and melphalan 140 mg/m²/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/m² if <60 years old or 250 mg/m² 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).

**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 3 consecutive days with an absolute neutrophil count ≥5 x 10^9/L. Platelet engraftment was defined as the first of 3 consecutive days with a platelet count ≥20 x 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.

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**Figure 1. Treatment plan.**

| Fludarabine | 30 mg/m²/day IV |
|--------------|----------------|
| Melphalan    | 140 mg/m²/day IV |
| Alemtuzumab  | 20 mg/day IV or subQ |
| Tacrolimus   | D-2 to D+180 |

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**Table 1.** Definitions

| Grade | Description |
|-------|-------------|
| 1     | Mild erythema, urticaria, rash, or pruritus |
| 2     | Moderate erythema, fever, or hypotension |
| 3     | Severe erythema, fever, hypotension, or death |
| 4     | Anaphylaxis |

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**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.
viremia occurred in 10 patients in the subQ arm and 8 patients in the i.v. arm. CMV viremia was signiﬁcantly shorter in the subQ arm than in the i.v. arm (166 versus 350 days, P = .044; respectively). There was only 1 patient in the subQ group who developed post-transplantation lymphoproliferative disorder. Death due to a fatal infection occurred in 1 patient in the subQ arm and 2 patients in the i.v. arm. Fatal infections included *Escherichia coli* bacteremia with concomitant Coronavirus in the subQ arm and viridans group *Streptococcus* bacteremia and vancomycin-resistant *Enterococcus* bacteremia in the i.v. arm.

**Engraftment and Immune Reconstitution**

There was no difference in time to engraftment for neutrophils between the 2 arms; however, median time to platelet engraftment was shorter for the subQ cohort than the i.v. cohort (15 days versus 19 days, P = .037). In the i.v. cohort, 1 patient did not engraft both neutrophils and platelets and 4 patients who did not recover platelets.

### Table 2

**Baseline Characteristics**

| Characteristic                      | Subcutaneous (n = 26) | Intravenous (n = 20) | P Value |
|-------------------------------------|-----------------------|----------------------|---------|
| Age at transplantation, median (range), yr | 62 (40-73) | 60 (39-71) | .673    |
| Gender                              |                       |                      |         |
| Male                                | 15 (58)               | 11 (55)              | .555    |
| Female                              | 11 (42)               | 9 (45)               |         |
| Disease state                       |                       |                      | .494    |
| AML                                 | 15 (58)               | 11 (55)              |         |
| MDS                                 | 9 (35)                | 5 (25)               |         |
| Other                               | 2 (8)                 | 4 (20)               |         |
| Disease status at transplantation   |                       |                      | .029    |
| CR                                  | 8 (31)                | 7 (35)               |         |
| PR                                  | 1 (4)                 | 4 (20)               |         |
| SD                                  | 11 (42)               | 1 (5)                |         |
| PD                                  | 3 (12)                | 4 (20)               |         |
| Other                               | 3 (12)                | 4 (20)               |         |
| Prior stem cell transplantation     | 0                     | 3 (15)               | .075    |
| Sorror comorbidity score, median    | 3                     | 4                    | .434    |
| Karnofsky performance score, median | 80                    | 75                   | .062    |
| ASBMT risk category                 |                       |                      | .537    |
| Low                                 | 10 (38)               | 7 (35)               |         |
| Intermediate                        | 3 (12)                | 5 (25)               |         |
| High                                | 13 (50)               | 8 (40)               |         |
| CMV IgG seropositive                |                       |                      | .351    |
| Donor                               | 14 (54)               | 8 (40)               |         |
| Recipient                           | 17 (65)               | 14 (70)              | .741    |
| Gift source                         |                       |                      | .001    |
| Peripheral blood                    | 26 (100)              | 10 (50)              |         |
| Bone marrow                         | 0                     | 10 (50)              |         |
| Days to start of GCSF, median (range)| 10 (1-12)             | 10 (5-14)            | .311    |

*AML indicates acute myeloid leukemia; MDS, myelodysplastic syndrome; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; ASBMT, American Society for Blood and Marrow Transplantation; GCSF, granulocyte colony–stimulating factor.

Data presented are n (%), unless otherwise indicated.

* Others include follicular lymphoma, systemic mastocytosis, histiocytic sarcoma, non-Hodgkin lymphoma, myelofibrosis, and chronic neutrophilic leukemia.

**Table 1**

**Grading Criteria**

| Event                          | 1                          | 2                          | 3                          | 4                          | 5                          |
|-------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Infusion-related reaction     | Mild reaction, infusion     | Intervention not indicated  | Therapy or infusion         | Intervention indicated but  | Prolonged (eg, not rapidly   |
|                               | interruption not indicated  |                             | interruption indicated but   | responds promptly to         | responsive to symptomatic    |
|                               |                             |                             | symptoms promptly to         | symptomatic treatment       | medication and/or brief      |
|                               |                             |                             | recurrence of symptoms      |                             | interruption of infusion),   |
|                               |                             |                             | after initial improvement   |                             | recurrence of symptoms      |
|                               |                             |                             |                             |                             | after initial improvement    |
| Hypotension                   | Asymptomatic, intervention  | intervention not indicated  | Nonurgent medical           | Medical intervention        | Life-threatening consequences,|
|                               | intervention not indicated  |                             | intervention indicated       |                             | pressor or ventilatory       |
|                               |                             |                             | Life-threatening and urgent  |                             | support indicated, urgent    |
|                               |                             |                             | intervention indicated       |                             | intervention indicated       |
|                               |                             |                             | Death                       |                             | Death                       |

Grading according to the Common Terminology Criteria for Adverse Events/Cancer Therapy Evaluation Program, version 4.0.
of death in these patients included relapse (n = 1), multiorgan failure (n = 1), bacteremia (n = 1), and complications of engraftment failure (n = 2). In the subQ arm, 1 patient did not engraft both neutrophils and platelets. The cause of death for this patient was sepsis.

All evaluable patients were assessed for lymphocyte reconstitution at days -28, +100, and +180. The median lymphocyte counts on these days were identical for both the subQ and i.v. cohorts (1.1, 4.9, and 2.7 cells/µL). Mixed chimerism, defined as less than 90% donor chimerism, is common after alemtuzumab-based conditioning, but we found no difference between the 2 groups. For the i.v. group, 35%, 40%, and 40% of patients had <90% CD3 donor cells and 5%, 10%, and 20% had <90% CD33 donor cells at day +28, +100, and +180, respectively. For the subQ group, 38%, 58%, and 54% of patients had <90% CD3 donor cells and 0%, 12%, and 35% had <90% of CD33 donor cells at day +28, +100, and +180, respectively.

**GVHD**

Acute GVHD ≥ grade 2 was seen in 6 patients in the subQ arm and 3 patients in the i.v. arm (P = .711). Organs affected by acute GVHD included the gastrointestinal tract, skin, or both. Median time to onset of acute GVHD seemed shorter in the subQ arm than in the i.v. arm (64 days versus 220 days), but this difference was not statistically significant (P = .302). Chronic GVHD occurred in a small number of patients in each group and no patients in either group developed severe chronic GVHD. Median time to chronic GVHD was also similar between the 2 groups (341 versus 221 days, P = .221) (Table 4).

**Relapse and Survival**

There was no difference in the number of patients who relapsed or the time to relapse between the 2 cohorts (Table 4). Of the 10 patients who relapsed in the i.v. group, 6 patients died of progressive disease. In the subQ group, 6 of the 11 relapsed patients died from progressive disease. There was no difference in 30-day mortality or 1-year overall survival between the subQ and the i.v. group (0 versus 5%, P = not significant and 50% versus 50%, P = not significant). Causes of death in the i.v. arm included relapse (n = 5), fatal infection (n = 2), multiorgan failure (n = 1), and complications of graft failure (n = 2). Causes of death in the subQ arm included relapse (n = 6), pneumonia (n = 1), post-transplantation lymphoproliferative disorder (n = 1), acute respiratory distress syndrome (n = 1), and fatal infection (n = 1).

**DISCUSSION**

Each year, thousands of patients with hematologic malignancies undergo allogeneic stem cell transplantation, which offers a chance at cure. Acute and chronic GVHD are often severe, sometimes debilitating, and potentially deadly complications of transplantation. Alemtuzumab has been used successfully to prevent GVHD in allogeneic stem cell transplantations with positive long-term outcomes [5]. With the exception of recent data in pediatric patients who underwent transplantation for nonmalignant disease states, only the i.v. route of administration for alemtuzumab has been used in stem cell transplantation [12]. However, i.v. alemtuzumab has been associated with serious infusion-related reactions that include fever, chills, rigors, rash, hypotension, shortness of breath, bronchospasm, and anaphylaxis. Prevention of these reactions requires pretreatment with antihistamines, corticosteroids, and antipyretics. Here, we report our institutional experience with 46 patients in approximately a 2-year period, 20 of whom
received i.v. and 26 who received subQ alemtuzumab. We found a significantly lower rate of ≥grade 2 infusion-related reactions with subQ alemtuzumab compared with the i.v. route (8% versus 25%, \( P = .001 \)).

In all other respects, the outcomes of both groups of patients were remarkably similar. Incidences of acute and chronic GVHD were similar between the subQ and i.v. arms, indicating that subQ alemtuzumab may have similar efficacy to i.v. alemtuzumab in preventing GVHD. Only 1 patient in the subQ arm experienced grade 4 acute GVHD and no patients experienced severe chronic GVHD. This is consistent with most studies of i.v. alemtuzumab-containing regimens, which have observed an incidence of 10% to 20% acute GVHD and a low incidence of severe chronic GVHD [2,3]. We also did not observe a difference in risk of disease recurrence, nor did we notice an increase in the incidence of CMV or EBV reactivation. The number of infection-related deaths, most of them due to bacterial infections, was not significantly different between the patients given subQ versus i.v. alemtuzumab. Lastly, there was no differences in 30-day mortality and 1-year overall survival between patients in the subQ arm receiving peripheral blood stem cells and 50% of the patients in the i.v. cohort receiving bone marrow stem cells; however, this did not result in a statistically significant increased incidence of GVHD in the subQ cohort. Our analysis on engraftment is limited because of the differences in graft source. We continue to use subQ alemtuzumab and monitor data, as a long-term follow-up period is needed to assess outcomes such as overall survival and chronic GVHD.

In conclusion, this study, albeit retrospective, represents the first direct comparative analysis of subQ versus i.v. alemtuzumab in adult stem cell transplantation patients with hematological malignancies. No significant differences in infectious complications, relapse, GVHD, and survival were found between the 2 groups with the exception of a shorter median time to EBV viremia and platelet engraftment in the subQ arm. Transplantation centers utilizing i.v. alemtuzumab for GVHD prophylaxis may consider transitioning to subQ alemtuzumab. SubQ administration may lower infusion-related reactions compared with i.v. administration without jeopardizing efficacy of reducing GVHD.

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