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Impact of Alemtuzumab Scheduling on Graft-versus-Host Disease after Unrelated Donor Fludarabine and Melphalan Allografts

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A B S T R A C T

Alemtuzumab conditioning is highly effective at reducing the incidence of acute and chronic graft-versus-host disease (GVHD) in reduced-intensity fludarabine and melphalan transplantation with cyclosporine monotherapy. Less frequent and lower dose scheduling may be used with sibling donors, but an optimal regimen for matched unrelated donors has not been defined. In this retrospective observational study of 313 patients, the incidence and severity of GVHD was compared in patients receiving 3 different dose schedules: the standard 100-mg regimen (20 mg on days −7 to −3), 60 mg (30 mg on days −4 and −2), or 50 mg (10 mg on days −7 to −3). Patients treated with 100 mg, 60 mg, or 50 mg developed acute GVHD grades I to IV with an incidence of 74%, 65%, and 64%, respectively, whereas 36%, 32%, and 41% developed chronic GHVD. An excess of severe acute grades III/IV GVHD was observed in the 50-mg cohort (15% versus 2% to 6%; $P = .016$). The relative risk of severe acute grade GVHD remained more than 3-fold higher in the 50-mg cohort compared with the 100-mg cohort after adjustment for differences in HLA match, age, gender mismatch, cytomegalovirus risk, and diagnosis ($P = .030$). The findings indicate that the 60-mg alemtuzumab schedule was comparable with the 100-mg schedule, but more attenuated schedules may increase the risk of severe grade GVHD.

INTRODUCTION

Alemtuzumab (humanized anti-CD52 antibody) is highly effective at reducing the incidence of acute and chronic graft-versus-host disease (GVHD) in the setting of reduced-intensity transplantation with fludarabine and melphalan [1-7]. When delivered to recipients during conditioning therapy, it effects in vivo depletion of both recipient and donor T cells, natural killer cells, B cells, monocytes, and dendritic cells, owing to persistence in the recipient with a half-life of 8 days [8-11]. Freedom from GVHD is associated with partial chimerism of donor T cells, but this may be corrected with donor lymphocyte infusions to deliver good overall survival with minimal long-term morbidity [7,12-14].

The original fludarabine, melphalan, and alemtuzumab regimen used an empiric alemtuzumab schedule of 100 mg comprising five 20-mg doses given on consecutive days between days −7 and −3. This regimen is effective at abrogating GVHD in mixed cohorts of matched related and unrelated donor transplants used to treat patients with both myeloid and lymphoid malignancy [1-7]. It has also been noted that GVHD is well controlled in peripheral blood stem cell and bone marrow grafts from unrelated donors [15] and that a degree of antigen mismatching is well tolerated [16]. Similar schedules of alemtuzumab have also been used with other fludarabine-based reduced-intensity protocols with equivalent efficacy [14].

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Excessive T cell depletion may be associated with increased relapse and risk of infection [11,17-19], and several groups have shown that dose reduction is possible in unrelated donor transplantation. A number of schedules with doses of between 50 and 100 mg administered over 2 to 5 days have been tested [20-22], and it is reported that as little as 10 mg reduces the burden of GVHD [23]. A phased-dose de-escalation study in sibling transplants concluded that a single dose of 30 mg on day −1 was sufficient to reduce GVHD to a similar level as 100 mg of alemtuzumab [24], but a comparable study has not been performed using only unrelated donors in a common protocol. Retrospective comparison of 30-mg and 60-mg dosing in sibling and unrelated donor transplants, respectively, indicated that the unrelated cohort still experienced more GVHD and had higher donor T cell chimerism [25].

Owing to the long in vivo half-life of alemtuzumab, the total dose and scheduling both have the potential to modify GVHD risk substantially [11], but there is no consensus about an optimal regimen in fludarabine-melphalan unrelated donor transplantation. Here we report a retrospective observational study in which we compared 3 commonly used protocols. Reduction and compression of the alemtuzumab schedule to two 30-mg doses on days −4 and −2 was comparable with 100-mg doses between days −7 and −3, but patients receiving 50 mg alemtuzumab between days −7 and −3 were at greater risk of severe acute grades III/IV GVHD.

METHODS

Patients and Donors

Data were collated from 3 UK transplant centers: University College Hospital/Royal Free Hospital, University College London Hospitals NHS Foundation Trust, London; Northern Centre for Bone Marrow Transplantation, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne; and Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham. Sequential patients transplanted between January 2007 and December 2011 were included. Patients were over age 18 years at transplantation, had a hematologic malignancy at any stage, and were transplanted with an unrelated donor with at least 8/10 HLA 4-digit allele matching. The number of transplants with less than 10/10 matching was too small to discern differences between A, B, C, or DQ antigen mismatches. Peripheral blood stem cells were the major stem cell source at all centers. All patients gave consent for their clinical data to be reported anonymously according to local ethical approval. Clinical data were collected by transplant center data managers and analyzed by 3 authors (K.G., K.P., and M.C.).

Conditioning and Alemtuzumab Dosing

All patients were conditioned with 5 doses of fludarabine 30 mg/m^2 daily on days −7 to −3 and melphalan 140 mg/m^2 on day −2. GVHD prophylaxis consisted of cyclosporine monotherapy starting at 3 mg/kg/day adjusting to an initial level of at least 200 ng/mL. Each center delivered a different alemtuzumab schedule. London patients received 100 mg in five 20-mg daily doses given consecutively from days −7 to −3, Newcastle patients received 60 mg as two 30-mg doses on days −4 and −2, and Birmingham patients received 50 mg in five 10-mg doses given consecutively from days −7 to −3. Donor lymphocyte infusions (DLIs) were given for mixed chimerism in all centers according to 3 monthly escalating schedules starting at 6 months post-transplantation with a dose of 1×10^6 CD3$^+$ cells/kg. As the DLI schedule did not start until 6 months, it did not influence the incidence or severity of acute GVHD.

Study Endpoints and Supportive Care

The primary endpoints of the study were the raw incidence and severity of acute GVHD according to Seattle grading and the cumulative incidence of chronic GVHD. Secondary endpoints included donor T cell chimerism, cytomegalovirus (CMV) reactivation, nonrelapse mortality, relapse, and overall survival. Patients were assessable for acute GVHD if they survived until engraftment and for chronic GVHD if they lived more than 100 days. CMV reactivation was defined as more than 2 sequential blood PCR results $> 2 \times 10^3$ copies/mL or requiring anti-CMV therapy with ganciclovir, valganciclovir, or foscarnet. Antiviral prophylaxis was maintained with acyclovir 200 mg orally twice a day in the 100-mg cohort or 200 mg orally three times a day in the 60-mg and 50-mg cohorts.

Statistical Analysis

Analysis was performed according to European Group for Blood and Marrow Transplantation guidelines [26-29] on consecutive patients transplanted between January 2007 and December 2011. Chi-square and Mann-Whitney tests and Kaplan-Meier survival curves were plotted with GraphPad Prism 6 (La Jolla, CA) and cumulative incidence analysis with competing risks was performed with the cmprsk. function of the open-source software R. Kaplan-Meier curves were compared with log-rank (Mantel-Cox) tests, whereas cumulative incidence curves were compared with Gray's test. Patients were censored at last follow up. Multivariate analysis was performed in SPSS (IBM, Armonk, NY) using binary logistic regression (grades III/IV versus other).

RESULTS

Conditioning protocols used in this 3-center retrospective observational study are summarized in Figure 1. Both the scheduling and total dose of alemtuzumab was different between each cohort.

Patient Characteristics

Consecutive patients recruited at each center were included in the study. Several differences were noted in the patient characteristics reflecting local practice and referral bias, summarized in Table 1. Patients in each cohort were matched for donor cell source (90% to 97% receiving peripheral blood stem cells), HLA matching (69% to 83% at least 10/10), disease status, and follow-up. There were, however, significant differences in age, the proportion of female-to-male transplants, the frequency of high-risk CMV-positive recipients, and the distribution of disease between acute myeloid leukemia (AML) and lymphoproliferative disease. The 50-mg cohort had the highest rate of high-risk CMV serostatus (negative into positive, 25.23%; $P = .0058$), and patients were more likely to have a diagnosis of AML or myelodysplastic syndrome (MDS) (62.62%; $P = .0005$). Patients receiving 60 mg of alemtuzumab were younger (median age, 45; $P = .0051$) and had no female-to-male transplants ($P = .009$). Patients receiving 100 mg had the highest rate of female-to-male

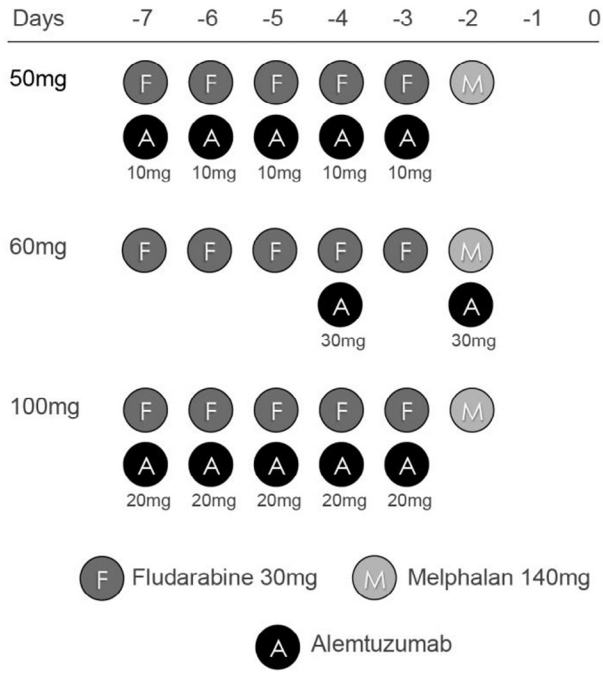

Figure 1. Preparative regimens. Outline of preparative regimens for the 3 patient cohorts.