A comparative study of reduced dose alemtuzumab in matched unrelated donor and related donor reduced intensity transplants

Laura Jardine,1,2 Amy Publicover,3 Venetia Bigley,1,2 Geoff Hale,4 Kim Pearce,1 Anne Dickinson,1 Graham Jackson2 and Matthew Collin1,2

1Institute of Cellular Medicine, Newcastle University, 2Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, 3University Hospital Southampton, Southampton, and 4Mablyte Ltd, Reading, UK

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Correspondence: Professor Matthew Collin, Human Dendritic Cell Laboratory, Institute of Cellular Medicine, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK.
E-mail: matthew.collin@newcastle.ac.uk

Summary

In vivo T cell depletion with 100 mg alemtuzumab prevents graft-versus-host disease (GVHD) in reduced intensity conditioned transplants but is associated with delayed immune reconstitution, a higher risk of infection and relapse. De-escalation studies have shown that a reduced dose of 30 mg is as effective as 100 mg in preventing GVHD in matched related donor (MRD) transplants. Dose reduction in matched unrelated donor (MUD) transplants is feasible but the comparative efficacy of alemtuzumab in this setting is not known and opinions vary widely concerning the optimal level of GVHD prophylaxis that should be achieved. Through retrospective analysis we made an objective comparison of MUD transplants receiving an empirically reduced dose of 60 mg, with MRD transplants receiving a 30 mg dose. We observed proportionate levels of alemtuzumab according to dose but an inverse relationship with body surface area particularly in MRD transplants. MUD transplants experienced more acute and chronic GVHD, higher T cell chimerism, more sustained use of ciclosporin and less need for donor lymphocyte infusion than MRD transplants. Thus, doubling the dose of alemtuzumab to 60 mg did not provide equivalent prevention of GVHD after MUD transplant although there was no difference in non-relapse mortality or survival compared with MRD transplants.

Keywords: bone marrow transplantation, T cell depletion, graft-versus-host disease.

Alemtuzumab (CAMPATH 1H), a humanised immunoglobulin G1 (IgG1) monoclonal antibody against CD52, is a well-established agent for effecting in vivo T cell depletion in the setting of allogeneic haematopoietic stem cell transplantation. By reducing the number of both donor and recipient T cells, it allows engraftment, while reducing the incidence of acute and chronic graft-versus-host disease (GVHD) (Kottaridis et al, 2000; Chakraverty et al, 2002). Conventional alemtuzumab dosing (100 mg in five daily doses of 20 mg) has been shown to ablareate acute and chronic GVHD almost completely in fludarabine and melphalan (FM) conditioned matched related donor (MRD) and matched unrelated donor (MUD) transplants (Kottaridis et al, 2000; Chakraverty et al, 2002). Conventional alemtuzumab dosing (100 mg in five daily doses of 20 mg) has been shown to ablareate acute and chronic GVHD almost completely in fludarabine and melphalan (FM) conditioned matched related donor (MRD) and matched unrelated donor (MUD) transplants (Kottaridis et al, 2000; Chakraverty et al, 2002). Subsequent studies have reported lower rates of chronic GVHD with equivalent overall survival compared with GVHD prophylaxis with methotrexate or mycophenolate mofetil (Perez-Simon et al, 2002; Delgado et al, 2008; van Besien et al, 2009; Malladi et al, 2009). This is achieved, however, at the expense of delayed immune reconstitution (Morris et al, 2003; Dodero et al, 2005), an increase in opportunistic infections (Chakrabarti et al, 2002a,b; Perez-Simon et al, 2002; Avivi et al, 2004) and higher incidence of mixed chimerism, which may impair graft-versus-leukaemia responses (Mackinnon et al, 1994).

The risks of T cell depletion can be ameliorated by donor lymphocyte infusions (DLIs) (Peggs et al, 2004, 2007; Bloor et al, 2008; Thomson et al, 2010; Mohamedbhai et al, 2012; Liga et al, 2013) but there is a need to define minimum levels of T cell depletion that provide effective protection from GVHD in different settings. A formal dose de-escalation study in MRD transplants concluded that a single alemtuzumab dose of 30 mg on day −1 is sufficient to prevent GVHD (Chakraverty et al, 2010) but equivalent studies in MUD transplants are lacking. Favourable outcomes...
have been reported in mixed cohorts of MRD and MUD transplants for a wide range of alemtuzumab doses from 50 mg to as little as 10 mg (Faulkner et al., 2004; Khouri et al., 2004; Tholouli et al., 2008; Bertz et al., 2009; Spyridonidis et al., 2011; Gartner et al., 2013; Potter et al., 2014). These are difficult to interpret: first, they involve mixed cohorts of MRD and MUD transplants; and second, the definition of ‘adequate’ control of GVHD is entirely subjective with some centres tolerating much higher rates of acute GVHD and extensive chronic GVHD than others.

In the absence of a formal de-escalation study in MUD transplants and lack of rational criteria to define adequate GVHD prophylaxis, we compared an empirically reduced dose of 60 mg alemtuzumab in MUD transplants, with 30 mg for MRD transplants, previously defined by formal study (Chakraverty et al., 2010). This offers an objective assessment of the potential of alemtuzumab to modify unrelated donor alloreactivity, relative to the level of a sibling donor.

**Methods**

**Study design and ethics**

The study included sequential patients transplanted with FM conditioning, following the introduction of de-escalated alemtuzumab dosing for MRD and MUD transplants in 2006. Clinical records were interrogated for GVHD, survival, chimerism testing and ciclosporin levels. All patients gave consent for clinical follow-up and post-transplant serum sampling for research purposes, according to protocols approved by the local research ethics committee of Northumberland and North Tyneside.

**Conditioning regimen and alemtuzumab dosing**

All patients received fludarabine 30 mg/m² per day from day −7 to −3 and melphalan 140 mg/m² day −2. Alemtuzumab 30 mg was given on day −2 for MRD transplants and on days −4 and −2 for MRD transplants (total 60 mg). Day −2 was preferred rather than day −1 because kinetic studies indicated a steep decline in levels in the first 24 h after infusion (Morris et al., 2003). We reasoned that the timing of stem cell infusion, which is not well controlled, would have less effect on the level of T cell depletion if we allowed 48 h following alemtuzumab administration, at which point alemtuzumab levels would be more stable. A minimum CD34⁺ stem cell dose of $4 \times 10^6$/kg was infused in all patients. Historical patients treated with 100 mg of alemtuzumab received 20 mg daily from day −7 to −3, inclusive.

**Post-transplant monitoring and management**

Graft-versus-host disease prophylaxis was ciclosporin given at 2-5 mg/kg twice daily from day −1 (with a target of 200–300 μg/l). Ciclosporin levels were monitored twice weekly by enzyme-linked immunosorbent assay. Tapering began at day +30 in the absence of GVHD. All patients received chemoprophylaxis against *Pneumocystis jirovecii* and Varicella Zoster. Serum cytomegalovirus (CMV) copy number was assessed twice weekly by polymerase chain reaction (PCR) and pre-emptive therapy was initiated if copy number rose above $10^4$. Peripheral blood and bone marrow chimerism was tested by short tandem repeat PCR on unfractionated bone marrow and magnetically-selected CD3⁺ and CD15⁺ fractions of peripheral blood. Monitoring took place monthly until day +100 and 3-monthly thereafter. A schedule of DLIs, escalating by half-log increments every 3 months was instituted for persistent partial chimerism, beginning at $3 \times 10^7$/kg at 6 months. Patients with early relapse received 10-fold higher doses at 4–6 weekly intervals. Clinical assessment of acute GVHD was performed at least once weekly in the first 100 d using modified Glucksberg criteria (Hunt et al., 2001). Incidence of chronic GVHD was assessed at 1 year post-transplant and graded using both Seattle and National Institutes of Health criteria (Shulman et al., 1980; Filipovich et al., 2005). Body surface area was estimated by the method of Dubois (Dubois & Dubois, 1916).

**Serum alemtuzumab measurement**

Post-transplant serum samples were available from 20 MRD recipients and 13 MUD recipients at day +1 and 11 MRD recipients and nine MUD recipients at day 3–4. Alemtuzumab concentration was measured as previously described by a validated flow cytometry assay (Rebello & Hale, 2002).

**Statistical methods**

Intergroup analyses were performed with Student’s *t* test for continuous variables, Mann–Whitney test for proportions and Chi-square for contingency. The three-group-comparison of serum alemtuzumab levels used one-way analysis of variance (*ANOVA*). Multiple *t*-tests used for intergroup analysis of serum ciclosporin levels over time were subjected to sequential Bonferroni correction. Overall survival was analysed by the Kaplan Meier method with log-rank test to compare survival curves. Relapse and non-relapse mortality were analysed by the cumulative incidence method with relapse as a competing event for non-relapse mortality (NRM) and vice-versa. Cumulative incidence curves were compared with Gray’s test. Hazard ratios were calculated by Cox Regression modelling. Graphing and statistical analyses were performed with GraphPad Prism version 6.0 (GraphPad Software, Inc. La Jolla, CA, USA) except for cumulative incidence, which was performed with R version 3.1.0 and Cox Regression, which was performed with SPS version 21 (IBM United Kingdom Ltd., Portsmouth, UK). *P* < 0.05 was recorded as significant.
*Transplant indication*  

- AML: 14 (58) 9 (47)  
- MDS: 2 (8) 1 (5)  
- NHL: 26 (52) 2 (11)  
- HL: 4 (11) 3 (16)  
- CML: 2 (4) 1 (5)  
- Myeloma: 0 3 (16)  
- Other: 0 3 (16)  

*Stem cell source*  

- PBSC: 18 (75) 15 (79)  
- BM: 6 (25) 4 (21)  
- CMV (donor/recipient)  
  - Negative/positive: 51 (21) 5 (22)  
  - Positive/negative: 2 (8) 2 (11)  
  - Positive/positive: 5 (21) 6 (32)  
  - Negative/negative: 2 (8) 2 (11)  

*FMA, fludarabine, melphalan, alemtuzumab; SEM, standard error of the mean; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; HNL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CML, chronic myeloid leukaemia; PBSC, Peripheral blood stem cells; BM, bone marrow; CMV, cytomegalovirus.*

cohorts, reaching significance in MRD transplants ($r^2 = 0.70$; $P < 0.0001$; Fig 2C,D).  

### Chimerism

Chimerism data were available for all ($n = 39$) patients evaluable at day +100. Median myeloid engraftment (CD15$^+$ cells) was 100% in both cohorts (not shown). Donor T cell engraftment (CD3$^+$ cells) was significantly higher in MUD than MRD recipients (median ± interquartile range: 88 ± 33 compared with 21 ± 46; $P = 0.0002$; Fig 3A). As a result of treating partial T cell chimerism pre-emptively in patients surviving more than 6 months, fewer MUD patients received DLI (4/19; seven doses in total) compared with MRD patients (20/24; 31 doses in total), $P < 0.0001$.

### Graft-versus-host disease

Overall, 13 out of 16 (81%) MUD recipients surviving to day +100 experienced acute GVHD compared with 1 out of 23 (4%) MRD recipients, $P < 0.0001$. GVHD grade II or greater occurred only in MUD recipients (44% vs. 0%, $P < 0.0001$) (Fig 3B). Similarly, chronic GVHD was more common in MUD recipients (55% vs. 20%; $P < 0.0001$) and more often extensive (Fig 3C).
**Immunosuppression**

Ciclosporin was tapered in the absence of GVHD from day +30. Increased GVHD in the MUD recipients was reflected by diverging mean serum ciclosporin concentrations from day +50. Overall, 13/16 (81%) MUD recipients still received ciclosporin at day +100 compared with 5/23 (22%) MRD recipients. Ciclosporin was completely withdrawn from all MRD recipients by day 128 but 7/16 (44%) MUD recipients still required immunosuppression.
The hazard ratio for relapse in MUD versus MRD recipients 2 years were 54% (31–72%) and 45% (18–69%) in MUD and MUD recipients, respectively (Fig 5C). The hazard ratio for death in MUD versus MRD recipients was 1.135 (95% CI 0.455–2.831), P = 0.785.

**Discussion**

The optimal dose of alemtuzumab for in vivo T cell depletion of reduced intensity conditioned transplantation is controversial and depends upon subjective judgments about the level of GVHD that tolerable or desirable, the perceived risk of relapse and the willingness of physicians to use pre-emptive DLI to bolster post-transplant immune reconstitution. The overall survival has been reported to be comparable between patients receiving widely ranging levels of in vivo T cell depletion (Perez-Simon et al, 2002; Delgado et al, 2008; van Besien et al, 2009; Malladi et al, 2009). The use of alemtuzumab is generally associated with higher relapse risk but less non-relapse death and proponents argue that the quality of survivorship is improved by the prevention of extensive chronic GVHD (Perez-Simon et al, 2002), particularly in the T cell compartment.

Here we have evaluated 60 mg dosing for MUD transplants relative to the 30 mg dose, defined as optimal for stringent control of GVHD in MRD transplants (Chakraverty et al, 2010). Monitoring of serum indicates that much lower levels are achieved than with 100 mg of alemtuzumab and that there is a predictable difference between 30 mg for MRD and 60 mg for MUD transplants, at day +1. We elected to give alemtuzumab 1 d earlier than Chakraverty et al (2010), at day –2, and the dose measured at day +1 was 30–40% lower than that reported on day 0 by these authors (2.9 μg/ml for 30 mg and 5.4 μg/ml for 60 mg in this study compared with approximately 5 and 7.5 μg/ml, respectively). However, this did not appear to increase the incidence of acute GVHD grades II–IV in our MUD cohort (both studies <5%). We also demonstrated a significant inverse relationship with BSA for MRD transplants and a trend in the same direction for MUD transplants. Metresquared dosing is common in paediatric practise (Dodero et al, 2005; Shah et al, 2007) and it is possible that more predictable outcomes would be observed if a similar approach was taken in adults (Morris et al, 2003; Chakraverty et al, 2010). The use of one 30 mg dose (two 30 mg doses for MUD transplants) in our schedule also makes economic sense, as 30 mg is the presentation vial size of the drug. One possible drawback is that the infusional toxicity of alemtuzumab may be higher with a single dose than with several fractionated doses, although we did not observe major difficulties with this. Prior commencement of fludarabine (day –7) before the first dose of alemtuzumab (day –4) may have reduced the incidence of infusional toxicity in these patients.

Our study is limited by the retrospective nature and relatively small number of patients transplanted over the period of observation. A prospective study would have been.
preferred but reduced alemtuzumab dosing in MUD transplants was already common practice, making a large prospective study, similar to that performed in MRD transplants, difficult to conduct. Comparison with the sibling cohort receiving 30 mg of alemtuzumab, rather than the historical MUD cohort receiving 100 mg, was motivated by the fact that sibling 30 mg and MUD 60 mg could be compared contemporaneously and that the most carefully annotated dose regime in the literature is the 30 mg dose given to siblings. The power of the study to detect differences in survival is rather low as indicated by wide confidence intervals in the hazard ratios. However, our primary aim was to report outcomes related to the control of GVHD. The observation that overall survival remains relatively constant with different levels of GVHD prophylaxis has been reported in several other studies (Perez-Simon et al, 2002; Delgado et al, 2008; van Besien et al, 2009; Malladi et al, 2009).

Mixed cohorts of MRD and MUD transplant patients treated with lower doses of alemtuzumab have satisfactory outcomes overall (Faulkner et al, 2004; Khouri et al, 2004; Tholouli et al, 2008; Bertz et al, 2009; Spyridonidis et al, 2011; Gartner et al, 2013; Potter et al, 2014). In a large series of 58 MRD and 69 MUD transplants subjected to a reducing regimen of 40, 20 and 10 mg of alemtuzumab, it was possible to infer differences between the response of MRD and MUD patients to alemtuzumab (Bertz et al, 2009). For example, MUD transplants receiving 40 mg experienced 27% grade II–IV GVHD compared with MRD patients receiving 10 mg who only experienced 10% grade II–IV. This suggests that unrelated donors cause significantly more alloreactivity in this range of alemtuzumab dosing. In support of this, we found that 44% of MUD transplants experienced grade II–IV acute GVHD after 60 mg of alemtuzumab compared with 0% of MRD patients after 30 mg of alemtuzumab. Both reports are consistent in finding more acute and chronic GVHD with MUD transplants, even when alemtuzumab dosing was increased by several fold.

In keeping with higher rates of GVHD, we observed higher donor T cell chimerism at day 100 in MUD transplants and recorded lower use of DLI compared with MRD transplants managed with the same pre-emptive DLI policy. Higher indices of alloreactivity in MUD transplants were not due to more aggressive withdrawal of immunosuppression, as higher ciclosporin levels were maintained in these patients after day 50. Survival, relapse and non-relapse outcomes were comparable as in other studies. One limitation of this report is that we did not record quality of life, which may have been relatively impaired in MUD transplants owing to a higher rate of extensive chronic GVHD.

Our data suggest that 60 mg of alemtuzumab does not achieve equivalent control of GVHD compared with 30 mg in MRD transplants. However, it may be naive to assume that an ‘equivalent’ dose can be reached by simple titration. Review of MUD transplant patients receiving the original 100 mg dose indicates a 20% incidence of acute GVHD grades II–IV (Mead et al, 2010). Notably, this level of acute GVHD is still above that reported for MRD transplants with 30 mg dose (0–5%) and only marginally increases to 22% when mismatching is permitted in unrelated donors (Mead et al, 2010). These observations suggest that the relationship between alemtuzumab dose and antigenic disparity is non-linear and that it may not be possible to achieve equivalent...
GVHD prophylaxis between MUD and MRD transplants simply by dose adjustment. Fortunately, as many studies illustrate, overall survival often remains stable despite significant variation in the burden of GVHD (Perez-Simon et al. 2002; Delgado et al. 2008; van Besien et al. 2009; Malladi et al. 2009). Further improvements in outcome may yet be achievable by paying close attention to individualised dosing of alemtuzumab based on BSA, expression of CD52 by malignant cells and the risk of graft rejection or relapse (Khouri et al. 2004; Chakraverty et al. 2010: Mead et al. 2010). Attention to long-term quality of life measurements is also paramount.

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Authorship

Laura Jardine performed the research, analysed the data and wrote the paper. Amy Publicover analysed data and wrote the paper. Venetia Bigley acquired clinical data. Geoff Hale performed research and contributed data. Anne Dickinson interpreted data. Graham Jackson acquired clinical data. Matthew Collin designed the research study, analysed data and wrote the manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

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