Reduced intensity conditioning T depleted allogeneic transplants in AML: Are there any factors predicting favourable outcomes?

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ABSTRACT: Reduced intensity conditioning (RIC) regimens permit the extension of a potentially curative graft-versus-leukemia effect to older patients with acute myeloid leukemia (AML) whose outlook with conventional chemotherapy would be poor. T cell depletion using alemtuzumab reduces the risk of severe graft-versus-host disease (GVHD) after RIC allografts but may compromise anti-leukemic activity. We have therefore analyzed which factors predict long term survival in 65 patients with AML transplanted using an alemtuzumab based RIC regimen. The 100 day transplant related mortality for the whole cohort of patients was 10%. 30% of patients developed Grade II-IV acute GVHD and 21% chronic GVHD. The 3 year overall survival was 47%. Survival was significantly influenced by status at transplant (p = 0.002), presentation cytogenetics (p = 0.03) and the presence of a molecular mismatch at Class I or II HLA alleles in patients transplanted using an unrelated donor (p = 0.001) but not by age. Alemtuzumab based RIC regimens have the capacity to deliver sustained remissions in older patients with AML with a modest risk of GVHD but patients with active disease at the time of transplant or adverse cytogenetics require novel transplant strategies. Alternative stem cell sources should be considered in patients lacking a sibling or molecularly matched unrelated donor.

Key Words: Reduced intensity conditioning allogeneic transplants, Alemtuzumab, Acute Myeloid Leukaemia (AML).

INTRODUCTION

The incidence of AML rises sharply in adults over the age of 50. Although advances in chemotherapy and stem cell transplantation (SCT) have improved the outcome of children and younger adults there have only been modest improvements in the survival of older patients in the past three decades.¹-³ More effective anti-leukemic therapies are therefore urgently required in this sizeable patient population.

Allogeneic transplantation using a myeloablative conditioning regimen has been shown to represent the most effective form of anti-leukaemic therapy in adult AML and improves both disease free survival (DFS) and overall survival (OS) compared with standard chemotherapy in younger patients but is contra-indicated in older patients because of excessive transplant toxicity.⁴,⁵ The advent of reduced intensity conditioning (RIC) regimens has led to the possibility that it may be possible to extend the curative potential of allogeneic transplantation to older patients with AML in whom it was previously contra-indicated on the grounds of age or co-morbidity.⁶-⁸ Whilst it is incontestable that RIC regimens have reduced the immediate toxicity of allografting there remains a significant risk of acute and chronic graft-versus-host disease (GVHD) in patients transplanted with a T replete stem cell inoculum. As a result GVHD now represents the major cause of morbidity and mortality after a RIC transplant and significantly limits both the potential for post-transplant immunotherapy as well as the possibility of transplanting frailer patients.⁹,¹⁰,¹¹ It is now clear that administration of T cell depleting antibodies such alemtuzumab or anti-thymocyte globulin, reduces the risk of both acute and chronic GVHD without...
compromising engraftment in patients transplanted using a reduced intensity regimen\textsuperscript{12-15}. However, there remain concerns that depletion of T cells from the stem cell inoculum may compromise the ability of RIC allografts to deliver durable remissions\textsuperscript{14,16,17}. In order to define more clearly the potential role of alemtuzumab-based reduced intensity regimens in the management of AML we have analyzed the factors determining survival in 168 patients transplanted over a ten-year period.

**PATIENTS AND METHODS**

**Patients**

67 patients with AML were transplanted using a fludarabine/melphalan/alemtuzumab RIC regimen from February 1997 to June 2007. Patients whose outcome with chemotherapy was deemed to be poor and in whom a myeloablative conditioning was contra-indicated on the grounds of age, co-morbidity, or patient choice were eligible. The median age was 54 years (range 18-71 years). 35 patients were 60 years of age or over. 37 patients received an allograft from an unrelated donor and 30 from a matched sibling donor. 50 patients were in remission at the time of transplant (CR1 = 32, CR2/CR3 or beyond = 17). 18 patients had relapsed or refractory disease. The results of presentation cytogenetic analysis were available for 64 patients and risk stratification was performed using MRC criteria\textsuperscript{18}. 24 patients were classified as intermediate risk at diagnosis. 16 patients had adverse risk cytogenetics.

**Transplant details and monitoring:**

The conditioning regimen incorporated fludarabine (30 mg/m\textsuperscript{2}/day for 5 days) melphalan (140 mg/m\textsuperscript{2} for 1 day) and alemtuzumab (10-20 mg/day for 5 days) as previously reported\textsuperscript{12,13}. Cyclosporin was used as GvHD prophylaxis at an initial dose of 5 mg/kg/day with the aim of discontinuing administration at day 90. Patients were enrolled after written informed consent had been obtained. Unrelated donor selection was performed according to published criteria and involved molecular typing for Class I (HLA-A and HLA-B, HLA-C) and Class II (DRB1 and DQB1) alleles. 6 patients underwent transplantation from an unrelated donor with an antigenic mismatch at Class I or II alleles. There was no evidence to suggest that patients receiving mismatched unrelated donor grafts constituted a demographically distinct population. Unrelated donors gave written consent through the current accepted standards and procedures of the relevant registry. The source of stem cells was peripheral blood (PBSC), collected after treating donors with granulocyte-colony stimulating factor (10 µg/kg/d for four days) in 62 patients, or bone marrow mononuclear cells in 5 (3 VUD, 2 sibling). The median CD34\textsuperscript{+} cell dose in patients allografted with PBSC was 5.3 x 10\textsuperscript{6} CD34\textsuperscript{+} cells/kg (range 1.3-15.8). The median mononuclear cell dose in recipients of bone marrow cells was 4.3 x 10\textsuperscript{8} mononuclear cells/kg (range 0.7-20.1).

Anti-microbial prophylaxis was determined by local protocols but all patients received prophylactic trimethoprim/sulfamethoxazole or nebulised pentamidine as prophylaxis against Pneumocystis jirovecii pneumonia. If either patient or donor were seropositive for cytomegalovirus (CMV) pre-transplant, plasma specimens were monitored weekly for evidence of CMV re-activation by PCR analysis post-transplant until 100 days post-transplant. Patients with evidence of CMV re-activation received pre-emptive therapy with ganciclovir.

Chimerism studies were performed on whole blood or bone marrow and a T cell-purified subfraction at 3 months post-transplant in a proportion of patients. Donor engraftment was assessed by fluorescence in situ hybridisation (FISH) or variable tandem repeat polymorphism analysis by polymerase chain reaction (PCR). Full donor chimerism was defined as the presence of >95% donor cells by FISH or PCR. Donor lymphocytes were administered in a number of patients either as management of mixed hemopoietic chimerism or at disease relapse.

**Outcomes and statistical analysis:**

Long term follow-up data is available on all patients. The median duration of follow-up in alive patients is 31 months (range 6-105 months) and 34 patients were transplanted three years or more prior to the final data analysis. Two patients died before day 28 and were excluded from analysis of engraftment kinetics. The main end-points of the study were OS, DFS and time to relapse. Survival curves were constructed using the method of Kaplan and Meier\textsuperscript{19} and the log-rank
test\(^{20}\) was used to assess differences between groups. OS was measured from the time of transplantation until death from any cause; DFS was measured from transplantation until disease-relapse or death. Patients still alive at the time of the analysis were censored at date of last follow-up. Time to relapse was calculated from date of transplant to date of first relapse; patients who did not relapse were censored at either date of death or date of last follow-up as appropriate. Minor end-points were transplant-related mortality (TRM) at 100 days and one year post-transplant and acute and chronic GvHD. TRM was defined as death in CR or death related to transplantation where it was not possible to assess disease status prior to death. Univariate analyses of the association of various clinical risk factors (sex, age, disease status, cytogenetics, donor type and GvHD) with these post-transplantation outcomes were calculated using univariate Cox regression analyses\(^{21}\). Multivariate analyses were performed using forward stepwise Cox proportional hazards regression to determine independent predictors of OS, DFS, TRM and time to relapse in patients allografted for AML. All factors found to have a p value of <0.1 in the previous univariate analysis were included in a multivariate analysis. Tests of significance were two-sided and had a significance level of 0.05 or less. Patients who died from other causes were censored at the time of death. Data were analyzed using the statistical software SAS (SAS Institute, SAS Circle, North Carolina, USA). For OS and DFS, risk factors found to be significant in multivariate analysis were used to generate a risk score for each outcome. These risk scores are variables free from subjective interpretation providing a more clear-cut basis for advising on an individual patient basis.

**RESULTS**

*Engraftment and Chimerism*

65 of the 67 patients engrafted. The median time to acquisition of an absolute neutrophil count > 0.5 x 10\(^9\)/l was 14 days (range 7-25 days). The median time to acquisition of a platelet count > 50 x 10\(^9\)/l was 16 days (range 7-66 days). Primary graft failure was documented in two patients-both recipients of unrelated grafts. The results of day 90 chimerism studies are available for 62 patients. 46 patients demonstrated full donor chimerism in whole blood and 40 in the T cell fraction. 13 patients demonstrated mixed chimerism in whole blood and 22 mixed chimerism in the T cell fraction at day 90.

**Overall survival**

At the time of analysis, 34 (50%) patients were alive. The 3-year probability of OS for the entire group of patients was 47% (95% CI, 38% to 55%). The 3 year OS for patients transplanted in CR1 or CR2/CR3 was 50% (95% CI, 38% to 62%) and 49% (95% CI, 34% to 61%) respectively compared to 17% (95% CI, 3% to 40%) for patients with relapsed/refractory disease. The 3 year OS for patients with intermediate risk cytogenetics was 53% (95% CI, 42% to 62%) compared with 31% (95% CI, 17% to 45%) for patients with adverse risk cytogenetics. There was no impact of patient age on OS. Patients aged under 60 years had a 3 year OS rate (48%) comparable to patients 60 years old or over (46%) (p = 0.31). No difference was noted in outcome between patients receiving an allograft from a volunteer unrelated donor and those using a sibling donor (p = 0.39). However in patients transplanted using an unrelated donor the presence of an antigenic mismatch at a class I or II allele was associated with an inferior outcome compared with patients receiving a transplant from a donor with no detectable HLA disparity (3 year OS 11% v 58%, p < 0.001). Alemtuzumab dose did not impact on the rate of overall survival.

In univariate analysis, adverse risk cytogenetics and active disease at the time of transplant were associated with a lower OS. Multivariate analyses showed both relapsed/refractory disease (HR, 1.4; 95% CI, 1.1-1.9; p = 0.002) and adverse-risk cytogenetics (HR, 2.1; 95% CI, 1.4-3.3; p = 0.03) to be associated with a lower OS (Table 2a). In addition, for the subgroup of patients transplanted using an unrelated donor, multivariate analysis showed the use of a mismatched donor to be associated with poorer OS (HR, 2.8; 95% CI, 1.5-5.3; p = 0.001) (Table 2a).

**Disease free survival**

The 3-year probability of DFS for the whole group was 43% (95% CI, 35%-52%). The 3 year DFS for patients transplanted in CR1 or CR2/CR3 was 49% and 40% respectively. The 3 year DFS for patients
with intermediate risk cytogenetics was 49% (95% CI, 39% to 59%) compared to 28% (95% CI, 15% to 43%) for patients with adverse risk cytogenetics. The three year DFS for patients transplanted using a molecularly matched unrelated donor was 50% (95% CI, 36%-63%) compared with 11% (95% CI, 2%-29%) for patients transplanted using a mismatched unrelated donor.

In univariate analysis, the variables associated with a lower DFS were relapsed/refractory status at the time of transplant and adverse risk cytogenetics. Multivariate analysis demonstrated that relapsed/refractory disease status (HR, 2.6; 95% CI, 1.5-4.7; p = 0.001) and adverse-risk cytogenetics (HR, 1.9; 95% CI, 1.2-2.9; p = 0.007) were associated with a lower DFS (Table 2b). Patients transplanted using a mismatched unrelated donor had a lower DFS (HR, 2.2; 95% CI, 1.2-4.2; p = 0.01) (Table 2b).

**Disease relapse**

Disease relapse occurred in 20 (29%) patients and represented the major cause of patient death (49% of all deaths). The median time to relapse was 6.5 months (interquartile range, 4-10 months). 45% of patients who relapsed did so in the first 6 months following transplantation. 82% of patients destined to relapse had done so within one year post-transplant. 31% (95% CI, 22% to 42%) of patients with intermediate risk cytogenetics transplanted in remission relapsed compared to 64% (95% CI, 39% to 88%) of patients with adverse risk cytogenetics transplanted in remission (P = 0.01). The 1-year relapse risk for those transplanted in CR was 33% (95% CI, 25%-40%) compared to 59% (95% CI, 35%-85%) for those with relapsed/refractory status. There was no difference in relapse risk between recipients of sibling and unrelated donor transplants (p = 0.77). Development of acute or chronic GVHD did not influence relapse rates (p = 0.6 and p = 0.2 respectively). Alemtuzumab dose did not impact on the incidence of disease relapse (p = 0.16). 9 patients received DLI as treatment for mixed chimerism (n = 3) or disease relapse (n = 6). 7 patients who received DLI died of relapsed disease.

In univariate analyses the factors associated with disease relapse were adverse-risk cytogenetics (p = 0.03) and the presence of relapsed/refractory disease at the time of transplant. In multivariate analysis, the only risk factor associated with disease relapse was relapsed/refractory disease (HR, 3.0; 95% CI, 1.4-6.5; p = 0.004) (Table 2c).

**GVHD and Transplant Related Mortality**

19 patients (30%) developed Grade II-IV acute GVHD. 5 (7%) patients developed Grade III-IV acute GVHD. 14 patients (21%) developed chronic GVHD. 11 patients (16%) developed limited chronic GVHD and

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<th>Table 2b. Univariate and multivariate analyses of donor and patient factors predicting disease free survival.</th>
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Reduced Intensity Transplants in AML

Reduced Intensity Transplants in AML

3(4%) extensive chronic GVHD. Alemtuzumab dose did not impact on the incidence of acute or chronic GVHD (p = 0.1 and 0.5 respectively).

The day 100 TRM was 10% (95% CI, 7%-16%) and 17% (95% CI, 12%-24%) at one year post-transplant. The day 100 TRM in patients undergoing transplantation from a sibling donor was 7% compared with 13% from an unrelated donor (p = 0.28). The day 100 TRM in patients aged under 60 years was 9% compared to 16% in patients 60 years old or over (p = 0.18). The day 100 TRM in relapsed/refractory patients was significantly higher than in patients transplanted in CR (25% v 9%). Univariate analysis showed relapsed/refractory disease to be the only variable associated with higher day-100 mortality (HR, 2.4; p = 0.02) (Table 2d). In volunteer unrelated donors, univariate analysis demonstrated that the use of a mismatched unrelated donor was the only variable associated with an increased day 100 TRM (HR, 11.5, p = 0.002) (Table 2d).

Outcome modelling

A model predicting survival was constructed using status at transplant, cytogenetic status and donor match (sibling or molecularly matched unrelated donor versus mismatched unrelated donor) to provide a measure of prognostication in newly diagnosed patients. The risk score for each patient comprised the sum of the risk factors using the following criteria: 0 for CR

### Table 2c. Univariate and multivariate analyses of donor and patient factors predicting relapse risk.

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### Table 2d. Univariate analysis of donor and patient factors predicting 100 day transplant related mortality.

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### Table 3. 3 year probability of OS and DFS for patients with AML after RIC allogeneic transplantation according to prognostic score.

Risk was assigned according to the following model: Disease status at transplant: CR = 0, relapsed/refractory disease = 1. Presentation karyotype: intermediate risk cytogenetics = 0, adverse risk = 1. Patient:donor HLA disparity: HLA matched sibling or molecularly matched unrelated donor = 0, mismatched unrelated donor = 1.

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outcome of chronic GVHD was associated with an improved T replete RIC protocol in which the development did not correlate with overall survival or relapse risk. Studies will be of importance. For this reason the ongoing donor v no donor analyses planned in a number of international donor older than 65 providing they have a suitably matched donor. The lowest possible score on this scale is 0, corresponding to a CR patient with intermediate risk cytogenetics and a matched sibling or unrelated donor. The impact of the prognostic score on outcome is documented in Table 3.

DISCUSSION

This study confirms the ability of alemtuzumab based RIC allografts to deliver long term disease free survival, with a low risk of acute or chronic GVHD, in a substantial proportion of older patients with high risk AML. We have identified a number of host and donor characteristics associated with a good outcome using this T cell depleted reduced intensity regimen. As a contrary it has been possible to define a group of patients with AML who have a relatively poor outcome using an alemtuzumab based RIC regimen for whom novel reduced intensity transplant strategies will be required.

In multivariate analysis the major determinants of long term survival are disease status at the time of transplantation, presentation cytogenetics and the degree of donor:host HLA disparity. Importantly, and in stark contrast to myeloablative transplants in AML, no impact of age was seen on outcome and it may be that this regimen can be safely extended to patients older than 65 providing they have a suitably matched donor. The incorporation of these factors into a prognostic score assists in risk stratification as well as the identiﬁcation of patients with a poor outcome who would be suitable for future Phase II clinical studies. It is important to note that whilst our results report outcomes which compare favourably with conventional chemotherapy the extent, if any, to which patient selection has biased these results is difﬁcult to determine. For this reason the ongoing donor v no donor analyses planned in a number of international studies will be of importance.

Our observation that the development of GVHD did not correlate with overall survival or relapse risk contrasts with the results of previous studies using a T replete RIC protocol in which the development of chronic GVHD was associated with an improved outcome. A similar lack of correlation between GVHD and relapse risk has been reported using an alemtuzumab based reduced intensity regimen in Non-Hodgkin’s lymphoma. However our data clearly do not exclude the presence of a clinically signiﬁcant T cell mediated GVL effect occurring in the context of sub-clinical GVHD. Alternatively the existence of an anti-tumor response mediated by a cellular compartment which is not susceptible to depletion by alemtuzumab is possible. Consequently detailed analysis of the impact of alemtuzumab on the numbers and function of NK cells, T regulatory cells and other potential cellular effectors which may mediate a GVL effect post transplant is required. An alternative explanation for the apparent dissociation of GVHD and GVL in these patients is the possibility that CD52 is expressed on leukemic stem cells and that alemtuzumab has a direct anti-tumor effect similar to that postulated for gemtuzumab ozogamicin.

This study identifies a population of patients with AML whose outcome with an alemtuzumab based allograft is less favourable. It has previously been demonstrated that remission status is a critical predictor of relapse and survival after both myeloablative and reduced intensity allografts for AML. However although cytogenetic status has been shown to be an important predictor of outcome in patients transplanted using a myeloablative regimen the impact of presentation karyotype has not previously been examined in patients undergoing a reduced intensity transplant. In this study OS was signiﬁcantly decreased in patients with adverse risk cytogenetics at presentation. Despite this the 35% 3 year OS in patients with adverse risk cytogenetics who were transplanted in remission remains encouraging given the poor outcome of this group if treated with chemotherapy alone. Strategies which might decrease the risk of disease recurrence post-transplant include reducing the dose of pre-transplant alemtuzumab or decreasing the intensity of post-transplant immunosuppression by modifying the dose or duration of cyclosporin administered post-transplant. Alternatively, since remission status appears to be a major determinant of relapse risk, the role of additional cytoreductive therapy pre-transplant should be studied. Both of these approaches are embodied in the FLAMS regimen developed by Kolb and colleagues and the impact of these strategies should be further studied in the population of pa-
patients we have identified to be at a high risk of relapse in this study.

The role of adjunctive DLI in restoring a GVL effect and thereby decreasing relapse risk after T cell depleted RIC allografts remains unexplored. In this study only small numbers of patients received DLI and it is not possible to comment on its potential benefit. One of the major limitations of either prophylactic or pre-emptive DLI after RIC allografts is the high rate of severe acute GVHD associated with even modest lymphocyte doses in the first year post-transplant. Since the great majority of patients destined to relapse after a T depleted RIC allograft for AML will do so within the first year post-transplant, interventions which postpone relapse and allow DLI to be administered at a later time point may be of benefit. We have previously demonstrated that adjunctive post-transplant imatinib can effectively manipulate the kinetics of disease recurrence and thereby postpone the requirement for early DLI. Similar combinations of leukemic specific therapy should be explored after T cell depleted reduced intensity allografts in AML and the tolerability and activity of demethylating agents or flt3 inhibitors (in FLT3 itd positive AML) or will be of interest.

Comparable outcomes have previously been reported with sibling and unrelated donors in patients transplanted using a reduced intensity regimen. Indeed it has been suggested that there may be a benefit associated with the use of unrelated donors consequent upon a lower relapse rate. In this study whilst we confirm equivalence of outcome between recipients of HLA identical sibling donors and molecularly matched unrelated donors we have identified a distinct adverse effect on survival in patients transplanted using a molecularly mismatched unrelated donor. Since the majority of older patients will not have a matched sibling donor who is fit to donate stem cells most reduced intensity transplants in this population are likely to be performed using an unrelated donor. The adverse impact of HLA mismatch observed in this series will, if confirmed, limit the availability of suitably matched unrelated donors and attention will have to be given to alternative stem cell sources such as umbilical cord blood. In this context the encouraging results recently reported in patients with double cord blood transplants in older patients with high risk AML are of importance.

In summary this study has delineated a substantial population of older patients with AML in whom a T cell depleted reduced intensity allograft can deliver encouraging long term disease free survival with modest rates of GVHD. Prospective studies and a higher number of patients will be required to confirm whether transplantation is superior to chemotherapy in this group of patients. At the same time it is clear that a number of patient and donor characteristics can be used to identify patients in whom outcome with a T depleted RIC allograft is poor and for whom new transplant strategies are required.

ΠΕΡΙΛΗΨΗ: Οι αλλογενείς μεταμοσχεύσεις μυελού με μειωμένης έντασης χημειοθεραπεία (reduced intensity conditioning) και εκλεκτική αφαίρεση Τ λεμφοκυττάρων: Υπάρχουν παράγοντες που προβλέπουν ευνοϊκά αποτελέσματα;

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parágonetos που προβλέπουν τη μακρά επιβίωση σε 65 ασθενείς με οξεία μυελογενή λευχαιμία (AML) που μεταμοσχεύθηκαν με reduced intensity conditioning and alemtuzumab. Η σχετική με τη μεταμόσχευση θνησιμότητα των πρώτων 100 ημερών για ολόκληρη την ομάδα των ασθενών ήταν 10%. 30% των ασθενών ανεπτύχθηκε βαθμο ΙΙ-IV εξώ GVHD και 21% χρόνο GVHD. Η γενική επιβίωση στα 3 έτη ήταν 47%. Η επιβίωση επηρεάστηκε σημαντικά από την ύφεση της ασθένειας πριν τη μεταμόσχευση (p = 0.002), τον καρυότυπο (p = 0.03) και την παρουσία ενός μη συμβατού μοριακού συνδυασμού στα αλληλόμορφα γονίδια HLA κατηγορίας Ι ή ΙΙ στους ασθενείς που μεταμοσχεύθηκαν από μη συγγενή δότη (p = 0.001) αλλά όχι από την ηλικία. Οι βασισμένες στο Alemtuzumab αλλογενείς μεταμοσχεύσεις έχουν την ικανότητα να επιφέρουν την ύφεση της οξείας μυελογενούς λευχαιμίας (AML) με έναν μέτριο κίνδυνο GVHD (graft versus host disease) αλλά οι ασθενείς με την ενεργή ασθένεια κατά την διάρκεια της μεταμόσχευσης ή δυσμενή καρυότυπο απαιτούν νέες στρατηγικές μεταμόσχευσης και θεραπείας. Οι εναλλακτικές πηγές αρχέγονων κυττάρων θα πρέπει να εξεταστούν στους ασθενείς που στερούνται έναν συγγενή ή μη συγγενή δότη.

Λέξεις Κλειδιά: Αλλογενής μεταμοσχεύσεις μυελού με μειωμένης έντασης χημειοθεραπεία, Alemtuzumab, Οξεία μυελογενής λευχαιμία.

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