

ORIGINAL ARTICLE

Reduced-intensity allogeneic haemopoietic stem cell transplantation induces durable responses in patients with chronic B-lymphoproliferative disorders

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Thirty-six patients with chronic B-lymphoproliferative disorders (B-LPD) underwent reduced-intensity allogeneic transplantation (RIT) from HLA-identical related donors. Diagnoses included follicular ($n = 17$), mantle cell ($n = 9$) and small lymphocytic lymphoma ($n = 2$), and chronic lymphocytic leukaemia ($n = 8$). Median age at transplant was 51 years (range, 30–66) and time from diagnosis was 3.4 years (range, 0.3–9.5). At transplant, 28% were in CR, 36% were in PR and 36% were chemorefractory. Conditioning therapy included fludarabine and either cyclophosphamide ($n = 27$) or melphalan ($n = 9$). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin (CsA)/methotrexate ($n = 21$), CsA/mycophenolate mofetil ($n = 13$) or CsA alone ($n = 2$). Eight patients died owing to acute GVHD ($n = 3$), infection in association with chronic GVHD ($n = 4$) and intra-abdominal bleeding ($n = 1$). Treatment-related mortality was 8% at day 100, and 17 and 20% at one and two years, respectively. The cumulative incidence of grade II–IV acute GVHD was 58%, whereas limited and extensive chronic GVHD occurred in 25 and 56%, respectively. No patient has relapsed or progressed. At a median follow-up of 48 months, overall survival probability is 80% (95% CI, 67–93%). We confirm that RIT in chronic B-LPD can result in high and durable CR rates but with significant incidences of acute and chronic GVHD.

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Introduction

The chronic B-lymphoproliferative disorders (B-LPD), including follicular lymphoma (FL), mantle cell lymphoma

(MCL), small lymphocytic lymphoma (SLL) and chronic lymphocytic leukaemia (CLL), have generally been regarded as incurable by conventional chemotherapy. Allogeneic stem cell transplantation using myeloablative conditioning offers the potential for cure but is associated with considerable transplant-related mortality, ranging from 22 to 40%.^{1–5} Reduced-intensity transplantation (RIT) is designed to reduce transplant-related mortality, so enabling its use in older patients not usually considered eligible for an allogeneic procedure.^{5–9} The rationale for RIT relies on previous observations that administration of donor lymphocyte infusions (DLI) can overcome relapse in patients post-allograft, suggesting that a graft-versus-tumour (GVT) effect is responsible for at least part of the efficacy of allografting.^{10–13} Subsequently, several groups have designed less toxic conditioning regimens to facilitate engraftment and provide the opportunity for a GVT effect.^{6–8,14–16}

The degrees of myelosuppression and immunosuppression achieved with RIT are variable and are dependent upon the use of purine analogues, low-dose total body irradiation, dose intensity of cytotoxic agents and *in vivo* T-cell depletion with agents such as alemtuzumab.^{5–7,14–21} Accordingly, there are significant differences in the kinetics of donor engraftment, as well as in the rates of graft-versus-host disease (GVHD) and infectious complications associated with these regimens. Durable engraftment of allogeneic cells and persistence of the GVT effect are crucial in assessing the long-term impact of RIT.^{13,22} A number of recent studies have confirmed the efficacy of RIT among patients with relapsed/refractory FL, MCL and CLL, but vary with respect to the conditioning therapy, GVHD prophylaxis, length of follow-up and durability of responses.^{17,20–28} In this study, we report results of RIT among 36 consecutive patients with chronic B-LPD disorders and confirm high and durable complete response rates, in which the median follow-up duration is 4 years.

Patients and methods

Patients

Eligible patients were aged 18–70 years with recurrent FL, SLL, CLL or MCL after a prior response to conventional treatment. Patients were required to have a favourable

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performance status (ECOG ≤ 1) and no uncontrolled concomitant medical illness or active infection. Patients were considered suitable for RIT if they had failed prior therapy, had an HLA-compatible relative capable of donating filgrastim-mobilised peripheral blood stem cells (PBSCs) and exhibited adverse prognostic features such as chemorefractoriness, relapses following either previous autografts, purine analogues or high-dose cytarabine, and mantle cell histology. Three additional patients (9%) were transplanted in first or second partial response as they were considered by their treating physician to be at high risk of progression. Informed consent was obtained from all patients and donors.

Stem cell collection

Donors received subcutaneous filgrastim (G-CSF), either 10 $\mu\text{g}/\text{kg}$ once daily or 5 $\mu\text{g}/\text{kg}$ twice daily on days -4 to 0. Leukapheresis was performed on day 0 (\pm day $+1$) to collect more than 2×10^6 per kg CD34⁺ cells.

Conditioning regimen

Reduced-intensity conditioning therapy consisted of fludarabine 25–30 mg/m^2 daily by intravenous (i.v.) infusion over 30 min for 5 days (total dose 125–150 mg/m^2). In addition, patients received either (i) cyclophosphamide at doses of 60 mg/kg i.v. daily for 1 ($n = 5$) or 2 days ($n = 19$) or 1000 mg/m^2 i.v. daily for 2 days ($n = 3$), or (ii) melphalan 120–140 mg/m^2 i.v. for 1 dose ($n = 9$).

Supportive care and infection prophylaxis

Haemopoietic growth factors were not used routinely. Infection prophylaxis was similar for all patients. Antiviral prophylaxis consisted of either aciclovir or valaciclovir. Trimethoprim-sulphamethoxazole was given as Pneumocystis prophylaxis and fluconazole 400 mg daily either intravenously or orally until day 100 as antifungal prophylaxis. Cytomegalovirus (CMV) reactivation was monitored on a weekly basis using either CMV antigenemia or polymerase chain reaction (PCR) assay; pre-emptive therapy with ganciclovir was started after positive antigenemia or PCR assays.

Graft-versus-host-disease prophylaxis and grading

Prophylaxis of GVHD consisted of either of the following cyclosporin (CsA) 3 mg/kg per day, and mycophenolate mofetil (MMF) 1000 mg orally twice daily from day $+1$ to day $+30$ and reducing to zero over 30 days ($n = 13$); CsA 3 mg/kg and methotrexate (MTX) i.v. 10 mg/m^2 on day 1, and 5 mg/m^2 on days 3, 6, ± 11 ($n = 21$); or CsA alone ($n = 2$). All patients receiving CsA/MMF were conditioned with fludarabine and cyclophosphamide (120 mg/kg), whereas among those receiving CsA/MTX, 13 received fludarabine–cyclophosphamide and nine were given fludarabine–melphalan. In the absence of acute GVHD, CsA was weaned over a period of 4–12 weeks, commencing approximately day $+100$ post transplant.

Assessment of outcome

Confirmation of donor engraftment was made by chimaerism analysis of flow cytometrically sorted peripheral blood

T cells. Percentages of donor–recipient chimaerism were evaluated using PCR-based amplification of highly polymorphic short tandem repeat units unique to donors and recipients, with analysis by either polyacrylamide gel or capillary electrophoresis. For these two methodologies, full donor T-cell chimaerism was defined as $\geq 95\%$.

Study end points and statistics

Major study end points included non-relapse mortality (NRM), progression-free survival (PFS), overall survival (OS) and the incidence/severity of GVHD. Actuarial curves were estimated according to the Kaplan–Meier method, whereas differences between curves were estimated by the log-rank test. Fisher's exact test for categorical data was used to compare variables in 2×2 tables; the two-tailed test was performed in each case.

Results

Patient characteristics

Thirty-six consecutive patients were included over a 5-year period between July 1999 and July 2004 at two transplant centres in Australia. Baseline demographic data are detailed in Table 1.

Engraftment

Engraftment data are summarised in Table 2. One patient with CLL failed to achieve significant levels of donor chimaerism, despite conditioning and two separate DLIs. No other patient received DLI. Chimaerism analysis on peripheral blood T cells (defined by CD3) was available for the majority of patients. Among those patients who received CsA/MMF for GVHD prophylaxis, full donor T-cell chimaerism was seen by day 60 in nine of 12 patients assessed; for patients given CsA/MTX, full donor chimaerism was seen by day 60 in seven of 16 patients assessed ($P = 0.10$). At 1 year, the cumulative incidence of achievement of full donor T-cell chimaerism among evaluable patients in each of the above groups was 92% (11 of 12) and 94% (16 of 17) ($P = 0.80$), respectively.

Toxicity

Eight patients died of causes not related to relapse, with five deaths occurring in patients > 55 years of age. The causes of death were steroid-refractory grade IV acute GVHD ($n = 3$), late infection in association with immunosuppressive therapy for chronic GVHD ($n = 4$) and intra-abdominal bleeding following a liver biopsy ($n = 1$). The late infectious deaths included three patients with bacterial sepsis between 8 and 20 months post transplant and one patient with a fungal pneumonia 4 years post transplant. Three of the infectious deaths occurred in patients who were chemorefractory pre-transplant, whereas one had achieved a CR and three had achieved a PR post transplant. Other severe but non-fatal infectious complications included an aspergilloma requiring lung resection ($n = 2$) in the context of extensive chronic GVHD, influenza A in one patient and probable viral pneumonitis 10 months post transplant in another. The three patients with fatal

acute GVHD had received GVHD prophylaxis with either CsA/MMF ($n=2$) or CsA alone ($n=1$). There were no cases of veno-occlusive disease, grade 3 or 4 mucositis or

Table 1 Patient characteristics

Characteristic	Number
Number	36
Age (years), median (range)	50.6 (30.2–65.6)
Male/female	18/18
<i>Histology</i>	
FL	17
SLL	2
CLL	8
MCL	9
Prior no. of chemotherapy regimens, median (range)	3 (1–6)
Prior anthracyclines (%)	28 (78)
Prior rituximab (%)	20 (56)
Prior purine analogues (%)	19 (53)
Prior high-dose cytarabine (%)	11 (31)
Prior autologous transplant (%)	2 (6)
<i>Status at transplantation</i>	
CR (%)	10 (28)
PR (%)	13 (36)
Refractory (%)	13 (36)
LDH at transplant, mean (range)	254 (114–709)
Marrow involvement at transplant (%)	17 (47)
<i>Donor</i>	
Siblings	35
Matched relative	1
Years from diagnosis to transplant, median (range)	3.4 (0.3–9.5)
<i>Conditioning regimen</i>	
Flu/Cyclo	27
Flu/Mel	9
<i>GVHD prophylaxis</i>	
CsA/MTX	21
CsA/MMF	13
CsA alone	2

Abbreviations: CLL = chronic lymphocytic leukaemia; CR = complete response; CsA = cyclosporin; Cyclo = cyclophosphamide; FL = follicular lymphoma; Flu = fludarabine; GVHD = graft-versus-host disease; LDH = lactate dehydrogenase; MCL = mantle cell lymphoma; Mel = melphalan; MMF = mycophenolate mofetil; MTX = methotrexate; PR = partial response; SLL = small lymphocytic lymphoma.

Table 2 Engraftment data

Characteristic	Number	P-value
CD34 ⁺ stem cells $\times 10^6$ per kg	5.0 (0.9–18.9)	NA
Days to ANC $> 0.5 \times 10^9/l$: all patients	14 (8–22)	NA
<i>Days to ANC $> 0.5 \times 10^9/l$</i>		
CsA/MMF	12 (10–22)	
CsA/MTX	15 (8–20)	0.8
Days to platelets $> 20 \times 10^9/l$: all patients	14 (8–30)	NA
<i>Days to platelets $> 20 \times 10^9/l$</i>		
CsA/MMF	11 (8–25)	
CsA/MTX	14 (9–19)	0.4

Abbreviations: ANC = absolute neutrophil count; CsA = cyclosporin; MMF = mycophenolate mofetil; MTX = methotrexate. NA = not applicable. All values are expressed as median (range).

significant non-haematological organ toxicity. For all patients, the actuarial probability of NRM was 8% (95% CI, 0–17%) at day 100 and 17% (95% CI, 5–29%) and 20% (95% CI, 8–32%) at 1 and 2 years, respectively (Figure 1).

Graft-versus-host disease

All patients were evaluable for acute GVHD. The cumulative actuarial incidences of grade II–IV and grade III–IV acute GVHD were 58% (95% CI, 47–70%) and 33% (95% CI, 22–45%), respectively (Figure 2). Rates of grade II–IV GVHD for those receiving CsA/MTX and CsA/MMF were 55 and 67% ($P=0.60$), respectively; rates

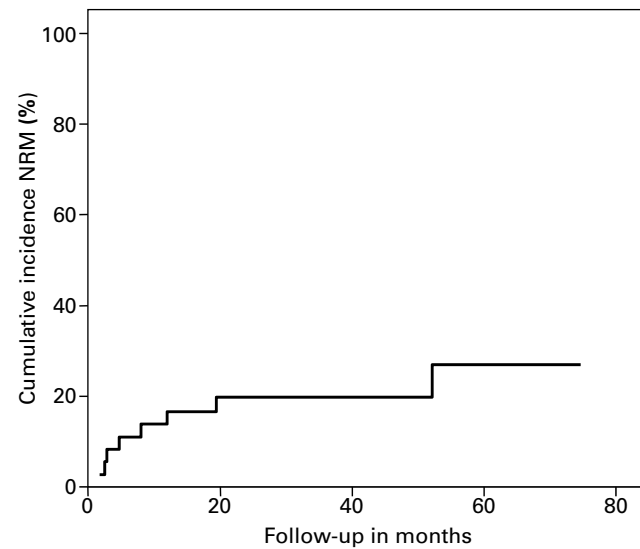


Figure 1 Cumulative incidence of non-relapse mortality (NRM) versus time for all patients.

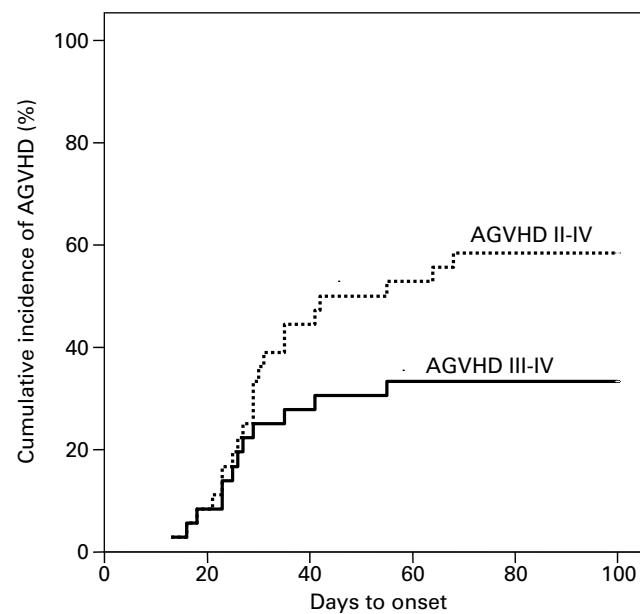


Figure 2 Cumulative incidence of acute GVHD grades II–IV (broken line) and III–IV (solid line) versus time.

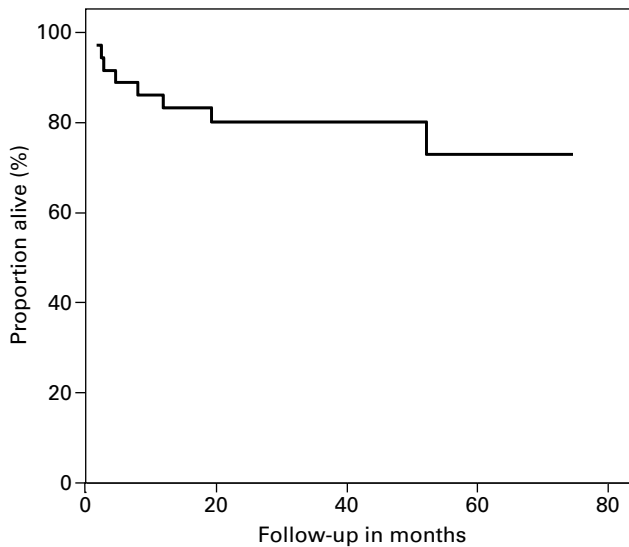


Figure 3 Progression-free and overall survival for all patients.

of grade III–IV GVHD were 23 and 42% ($P=0.36$), respectively. Chronic GVHD was seen in 26 of 32 evaluable patients including limited in eight (81%) and extensive in 18 (56%) patients. Four engrafting patients (three in CR and one in PR pre-transplant) experienced neither acute nor chronic GVHD.

Response

Maximum responses achieved post transplant in the 33 evaluable patients included CR in 29 (88%) and PR in three (9%), whereas one non-engrafting patient with CLL had stable disease (SD). Twenty-eight patients remain alive and in either CR ($n=27$) or with SD ($n=1$) at a median follow-up of 48 months (range, 13–75 months). Among the 13 patients with chemorefractory disease before transplant, two died of acute GVHD, three died of infection, whereas the remaining eight are alive in CR ($n=7$) or SD ($n=1$) at a median follow-up time of 56 months. Of the two previously autografted patients, one died of GIT haemorrhage in CR 12 months post transplant, whereas the second is alive in CR with limited chronic GVHD.

Progression-free and overall survival

To date, no patient has relapsed or progressed. The Kaplan–Meier estimate of the proportion of patients alive at a median follow-up of 48 months is 80% (95% CI, 67–93%) (Figure 3). Patients in CR or PR at transplant had an actuarial OS rate of 87% (95% CI, 72–100%) at a median follow-up of 42 months, whereas those with chemorefractory disease ($n=13$) at transplant had an estimated OS of 58% (95% CI, 28–87%) at a median follow-up of 56 months (Figure 4) ($P=0.14$). The estimated OS for patients with FL is 81% (95% CI, 62–100%) at a median follow-up of 43 months, 89% (95% CI, 68–100%) for patients with MCL at a median follow-up of 42 months and 56% (95% CI, 23–89%) for patients with CLL/SLL at a median follow-up of 56 months ($P=0.48$).

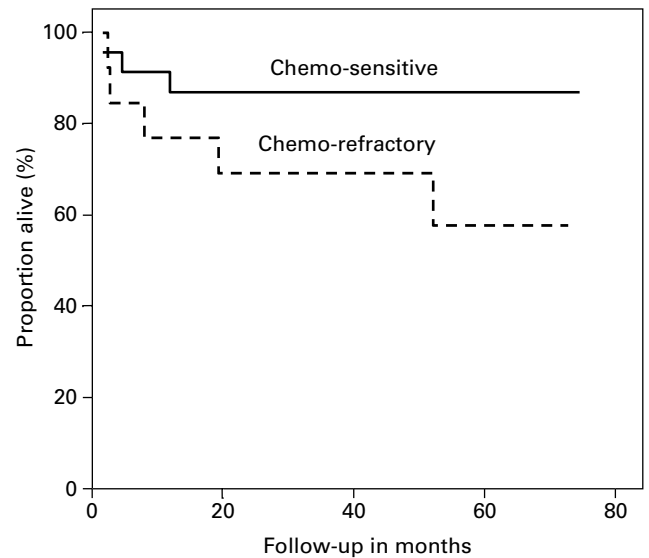


Figure 4 Overall survival by remission status at transplant: CR/PR ($n=23$) (solid line), chemorefractory ($n=13$) (broken line).

Discussion

We demonstrate high response rates and durable remissions among patients with chronic B-LPD disorders receiving RIT with fludarabine–cyclophosphamide or fludarabine–melphalan from HLA-compatible related donors. Conditioning therapy was well tolerated in this group of generally older, heavily pre-treated patients of whom more than half had received prior purine analogues, and of whom a third had chemorefractory disease before transplant. The NRM of 8% at day 100, and 17 and 20% at 1 and 2 years, respectively, is comparable with previous studies of similar patients treated with RIT regimens such as busulphan–fludarabine, melphalan–fludarabine or cyclophosphamide–fludarabine–thiotepa.^{7,9,16,18,24,26}

Nevertheless, this mortality is not trivial, and was almost entirely attributable to GVHD, either alone or in association with late infectious complications. Three patients died of steroid-refractory grade IV acute GVHD, whereas all four late infectious deaths and an additional two late fungal infections occurred in patients on immunosuppressive therapy for chronic GVHD. The observed incidences of grade II–IV acute GVHD (58%) and chronic GVHD (81%) were somewhat higher than those seen in other studies of RIT.^{5,6,9,14,16,25} These relatively high rates of acute and chronic GVHD may have resulted in part from the use of PBSCs, the conditioning regimens producing a high rate of full donor T-cell chimaerism and the GVHD prophylaxis with MMF or reduced-dose MTX.

The upside of the substantial rates of GVHD was the absence of disease progression. As a significant number of patients had active disease at the time of transplantation, our results support the concept that allogeneic GVT reactions after RIT play an important role in controlling disease recurrence and suggest that these GVT responses may be at least as critical as the contribution of the conditioning regimen. The apparent difference in estimated OS for those patients who were considered chemorefractory

(58%) before RIT compared to those in CR or PR (87%) at transplant was not significant and was essentially owing to the increase in the number of deaths as a result of either acute GVHD or late infection associated with chronic GVHD rather than to disease recurrence reported in other studies.^{17,21} It is tempting to speculate that these deaths in chemorefractory patients occurred in those who were more heavily pre-treated or immunosuppressed, as all had received three or more prior therapies including fludarabine. However, the numbers are too small to draw definitive conclusions. Notably, the use of non-T-depleted RIT conditioning as described here is not reliant upon DLI for the achievement of maximum response and overall disease control even among chemorefractory patients.^{19–21}

Optimal GVHD prophylaxis in RIT has not been established.^{13,22} Retrospective comparisons and prospective randomised trials comparing CsA/MTX and CsA/MMF as GVHD prophylaxis in myeloablative allografts indicate a shorter time to myeloid engraftment in those treated with MMF, without a difference in either OS, relapse rate, acute or chronic GVHD.^{29,30} In the current study, there appeared to be a trend towards faster engraftment, as defined by T-cell chimaerism, in those receiving MMF. Whereas there was no significant overall difference in rates of acute GVHD between the two groups, the three deaths from acute GVHD occurred in patients who had received either CsA/MMF or CsA alone. Difficulties with interpretation of any potential differences are confounded by the small sample size, and the complex interaction between GVHD prophylaxis and the conditioning therapies, which in this study included varying doses of both cyclophosphamide and melphalan.^{17,22}

Among patients undergoing RIT for B-LPD, results in FL have been the most encouraging, as observed rates of PFS and OS at 2 years have been as high as 84–95%.^{24,27} We report similarly favourable and relatively durable responses for 17 FL patients in whom the estimated PFS and OS was 81% at a median follow-up of 43 months. On the other hand, recent reports of RIT in patients with MCL have shown variable outcomes, with one EBMT series demonstrating a pattern of ongoing relapses, in contrast to two single institution studies of both chemosensitive and heavily pre-treated refractory patients, which have demonstrated relatively low risks of relapse.^{17,28,31} In the current study, eight (89%) of nine MCL patients are alive in CR post transplant, including two in PR and three chemorefractory patients pre-transplant.

Recent studies of RIT for the treatment of CLL have included patients with varying degrees of prior fludarabine exposure and chemorefractoriness, and with variable conditioning regimens. These studies have described encouraging rates of OS and DFS of 60–72 and 52–65%, respectively.^{27,32–34} We report a similar rate of OS of 56% for 10 CLL/SLL patients (of whom six were chemorefractory pre-transplant) at a median follow-up of 56 months. Again, all four deaths were due to late infections associated with chronic GVHD rather than to disease recurrence.

Our experience of RIT in B-LPD is consistent with a GVT effect and supports the use of this treatment modality even in patients with chemorefractory disease. Never-

theless, GVHD and its infectious sequelae remain a major obstacle to the safety and tolerability of this approach and suggest that further improvements in the outcome after RIT will depend predominantly on the reduction of the incidence of severe GVHD and improvements in post-transplant immune reconstitution.

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