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Reduced intensity allogeneic haematopoietic cell transplantation for chronic lymphocytic leukaemia: related donor and umbilical cord allografting

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chronic lymphocytic leukaemia; allogeneic transplantation; umbilical cord blood transplantation

Allogeneic haematopoietic cell transplantation (HCT) for chronic lymphocytic leukaemia (CLL) is increasingly used due to its incurability with conventional treatments, especially in patients with poor risk and multiply relapsed disease (Schetelig *et al*, 2003; Dreger *et al*, 2005; Sorror *et al*, 2005; Delgado *et al*, 2006). Reduced intensity conditioning (RIC) regimens may permit HCT with acceptable morbidity and mortality for older patients, though many still lack suitable human leucocyte antigen (HLA) matched related donors (MRD). Umbilical cord blood (UCB) has been shown to be an effective graft source for patients with haematological malignancies who need an allogeneic transplant but lack a MRD or unrelated donor (URD) (Majhail *et al*, 2008; Brunstein *et al*, 2009), yet only preliminary reports on its use are available for CLL (Rodrigues *et al*, 2009). We report our initial experience for CLL in patients undergoing RIC HCT from both MRD and UCB donors.

Twenty-six consecutive allogeneic transplants for CLL performed between 2000 and 2009 were analyzed. RIC HCT eligibility included either: age (≤ 55 years for MRD; >45 years for UCB), Karnofsky performance status ≥ 60%, organ dysfunction [ejection fraction (EF) ≥ 35%, carbon dioxide diffusion capacity (DLCO) ≥ 35%], or recent serious infection. Donors were either HLA-identical MRD ($n = 12$) or double UCB ($n = 14$) units matched at 4/6–6/6 HLA loci to recipients and to each other. All patients received cyclophosphamide (50 mg/kg intravenously day –6), fludarabine (40 mg/m² intravenously daily days –6 to –2)

and total body irradiation (200 cGy day⁻¹). Equine anti-thymocyte globulin (ATG) 15 mg/kg IV intravenously every 12 h for six doses days -3 to -1 was given to nine patients not receiving multi-agent chemotherapy within the preceding 3 months. Graft-versus-host disease (GVHD) prophylaxis was ciclosporin (CSA) dosed to trough levels of 200–400 ng/ml (days -3 to +180) plus mycophenolate mofetil (MMF) 1–1.5 g every 12 h (days -3 to +30) in all but one patient. Comorbidity scores (HCT-comorbidity index) were calculated retrospectively (Sorrer *et al*, 2005). Neutrophil recovery was defined as the first of three consecutive days with absolute neutrophil count $0.5 \times 10^9/l$. Platelet engraftment was defined as the first day of a sustained count $>20 \times 10^9/l$ without transfusion for 7 d.

Fludarabine resistance and poor risk cytogenetics were common (Table I), and all patients were heavily pretreated [median of 5.5 (MRD) and 4 (UCB) different regimens]. There were no significant differences in disease bulk, fludarabine resistance, or cytogenetic risks between patients receiving UCB versus MRD allografts (data not shown). Graft failure occurred in 3 (21%) UCB HCT cases. Two of these patients survive with autologous, non-CLL recovery, one 6 years and one 7 years after HCT. The proportion of patients with acute GVHD, grade III–IV at 100 days was 38% [95% confidence interval (CI) 20–57]. Cumulative non-relapse mortality (NRM) was 19% (95% CI 4–24%) at 100 days (Table II) and did not differ by pre-HCT comorbidity score (data not shown). Overall survival (OS) at 3 years was 51% (95% CI 29–68) while progression-free survival (PFS) at 3 years was 38% (95% CI 19–57). Following HCT, 10 of 12 (83%) MRD patients and 10 of 14 UCB patients (71%) achieved complete remission ($P = 0.65$). Relapse/progression at 1 year was 15% (95% CI 2–29%) and 25% (95% CI 8–42%) at 3 years.

These data indicate similar, but quicker neutrophil and platelet engraftment using MRD versus UCB grafts (Table II). The incidence of acute GVHD was similar, but there was a non-significant trend toward less chronic GVHD using UCB. NRM and PFS was similar at 3 years using either graft source but a trend towards lower OS was seen in the UCB cohort.

While URD HCT for CLL is accepted based on promising results reported by the Seattle and German groups (Schetelig *et al*, 2003; Sorrer *et al*, 2008), there remains limited data on UCB for CLL. A recent report described outcomes of patients with lymphoid malignancies undergoing RIC UCB HCT including 14 patients with CLL. One-year PFS and OS rates for CLL patients were 43% and 51%, respectively (Rodrigues *et al*, 2009), but limited data on GVHD, NRM or later outcomes was available.

As we reported, chronic GVHD is less frequent after UCB HCT, which, accompanied by limited risks of graft failure, infections and acute GVHD, could make it a preferred option (Majhail *et al*, 2008). Heterogeneity among patients and the small cohort prevent clear identification of factors contributing to lower OS seen in the UCB group. The small numbers also confound determination of the preferred timing for HCT for these heavily pre-treated patients. Earlier HCT may yield improvements in NRM and thereby increase OS compared to risks of ongoing salvage therapies (Keating *et al*, 2002). Alternative stem cell sources will be needed for the approximately 30–40% of patients without a well-matched related or URD (Brunstein *et al*, 2007). Our data indicate that allogeneic HCT can result in long-term remissions for heavily-treated CLL patients using either MRD or UCB HCT.

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Table I

Patient, disease and transplant characteristics.

Patient Characteristics (<i>n</i> = 26)	
Age, median (range), years	53 (43–67)
50 years, <i>n</i> (%)	20 (77)
Female:Male	4:22
Years from diagnosis to transplant, median (range)	6·2(2·3–12·1)
Disease characteristics at HCT	
Bulky disease (> 5 cm), <i>n</i> (%)	6 (23)
Fludarabine refractory, <i>n</i> (%)	12 (46)
Cytogenetics, <i>n</i> (%)	
Standard risk	13 (50)
Poor risk (del 11q, del 17p, complex)	11 (42)
Not tested	2 (8)
Prior regimens, median, (range)	4·5 (1–9)
Splenectomy, <i>n</i> (%)	7 (27)
Transplant characteristics	
Stem cell source	
MRD	12
UCB	14
Conditioning	
Cy/Flu/TBI [*]	17 (65)
GVHD prophylaxis	
CSA/MMF [†]	25 (96)
HCT – comorbidity index, <i>n</i> (%)	
Low/Intermediate risk (0–1)	10 (38)
High risk (> 2)	14 (54)
Unavailable	2 (8)
Median follow-up, years (range)	3·1(0·4–4·9)

MRD, matched related donor; UCB, umbilical cord blood; Cy, cyclophosphamide; Flu, fludarabine; TBI, total body irradiation; GVHD, graft versus host disease; CSA, ciclosporin; MMF, mycophenolate mofetil; HCT, haematopoietic cell transplant.

^{*} Anti-thymocyte globulin was included for 9 patients.

[†] 1 UCB recipient received sirolimus instead of CSA.

Table II

Transplant outcomes.

		<i>P</i> value
Time to neutrophil engraftment; median days (range)	11.5 (0-41)	
MRD	11 (0-13)	0.01
UCB	16 (6-41)	
Time to platelet recovery $>20 \times 10^9/l$; median days (range)	18 (0-66)	
MRD	17 (0-27)	<0.01
UCB	51 (34-66)	
Acute GVHD, grades II-IV %, (95% CI) at day 100	54 (33-74)	
MRD	58 (30-87)	0.92
UCB	50 (23-77)	
Chronic GVHD % at 1 year, (95% CI)	23 (7-41)	
MRD	36 (8-64)	0.63
UCB	14 (0-31)	
Non-relapse mortality %, (95% CI) at 1 year	23 (7-39)	
MRD	8 (0-23)	0.34
UCB	36 (11-61)	
Survival %, (95% CI) at 3 years	51 (29-68)	
MRD	71 (34-90)	0.05
UCB	33 (11-58)	
Progression-free survival %, (95% CI) at 3 years	38 (19-57)	
MRD	52 (20-77)	0.08
UCB	26 (7-51)	

MRD, matched related donor; UCB, umbilical cord blood; Cy, cyclophosphamide; Flu, fludarabine; TBI, total body irradiation; GVHD, graft versus host disease; CSA, ciclosporin; MMF, mycophenolate mofetil; HCT, haematopoietic cell transplant.