Prophylactic donor lymphocyte infusion reduces the risk of relapse and increases survival in patients with mixed T cell chimerism after reduced intensity allogeneic stem cell transplantation

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INTRODUCTION

This is the largest case-series reporting outcomes in patients who have received pre-emptive donor lymphocyte infusion (pDLI) for mixed T cell donor chimerism post reduced intensity allogeneic stem cell transplant (RIC allo-SCT).

Reduced intensity conditioning followed by allogeneic stem cell transplant results in less transplant-related mortality than myeloablative regimens[1] but the reduction in transplant related mortality is counterbalanced by an increased risk of mixed donor T cell chimerism which is associated with relapse. Pre-emptive donor lymphocyte infusion can be used to bring about conversion to full donor chimerism (FDC) and survival in those who reach FDC with DLI is comparable to those who reach FDC spontaneously.[1,2]

However, despite its efficacy, DLI is thought to be associated with substantial rates of graft versus host disease (GvHD) in the region of 30%.[3,4] Additionally, the biomarker of achieving FDC has not been formally shown to correlate with improved survival outcomes. Furthermore, the optimal dosing, schedule, and timing of pDLI is not clear. Here we describe outcomes in 122 patients who received pDLI for mixed chimerism.

KEY MESSAGES

72% patients converted to full donor chimerism (FDC)

Severe GvHD occurred in 10%

GvHD contributed to death in 5%

Mild GvHD prior not predictive of GvHD after pDLI

5 year overall survival probability: 71%

Conversion to FDC predicts survival

Median time from most recent pDLI to FDC: 92 days

Results: Patient and DLI characteristics

Characteristics		
Total number of patients	122	
Sex		
Male (%)	77	63.1
Female (%)	45	36.9
Median age (range)		
At transplant	57	20-71
At first DLI	58	20-73
Median time (months) (IQR)		
Follow-up	29.1	54.5
Transplant to DLI	7.8	1.6-148
Disease (%)		
AML	46	37.7
MDS	18	14.8
Lymphoma	40	32.8
ALL	10	8.2
Other	8	6.5
Donor type (%)		
Matched unrelated	57	46.7
Matched related	65	53.3
% donor T cell chimerism		
Prior to DLI (mean, SD)	48.4	27.9
After final DLI (mean, SD)	73.2	39.4
Most number of DLIs (%)		
1	43	35.2
2	45	36.9
3	23	18.9
4	8	6.6
5	3	2.5
Median dose by DLI cycle (CD3+ cells/kg) (range)		
1 (n =186)	$1x10^6$	$1x10^5$ – $5x10^7$
2 (n=78)	$1x10^6$	$5x10^5$ – $8x10^7$
3 (n=34)	$1x10^7$	$1x10^6$ – $1x10^8$
4 (n=11)	$5x10^7$	$5x10^7$ – $1x10^8$
5 (n=3)	$1x10^8$	$5x10^7$ – $1x10^8$
Median cumulative DLI dose (CD3+ cells/kg) (range)	$6x10^6$	$1x10^6$ – $2.1x10^8$

Table 1. Patient characteristics

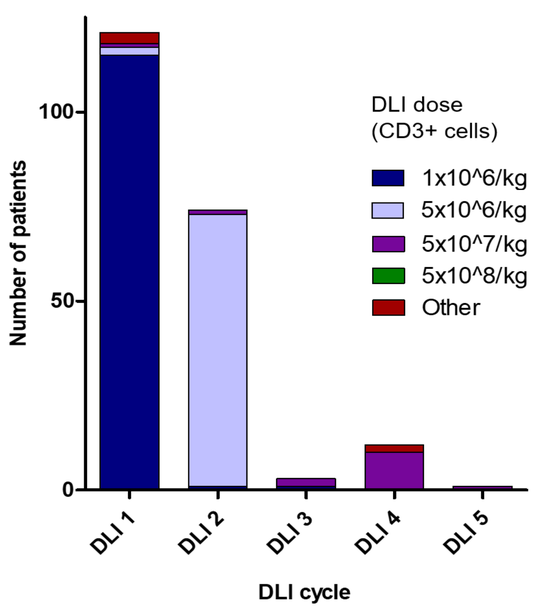

Figure 1. pDLI dose according to cycle

Median age: 58y

Median time transplant to pDLI: 7.8 months

Starting dose: 94% $1x10^6$ CD3+ cells per kg

Toxicity

Grade of GvHD	Number of patients (%)
Grade I acute or mild chronic	11 (9.0)
Grade II acute	13 (10.7)
Grade III acute or moderate chronic	4 (3.2)
Grade IV acute or severe chronic	8 (6.5)
Total	34 (27.9)

Table 2. Incidence of GvHD according to severity

GvHD contributed to death in 5%

71% required systemic treatment

Median onset was 55 days after first pDLI

No patients experienced graft aplasia

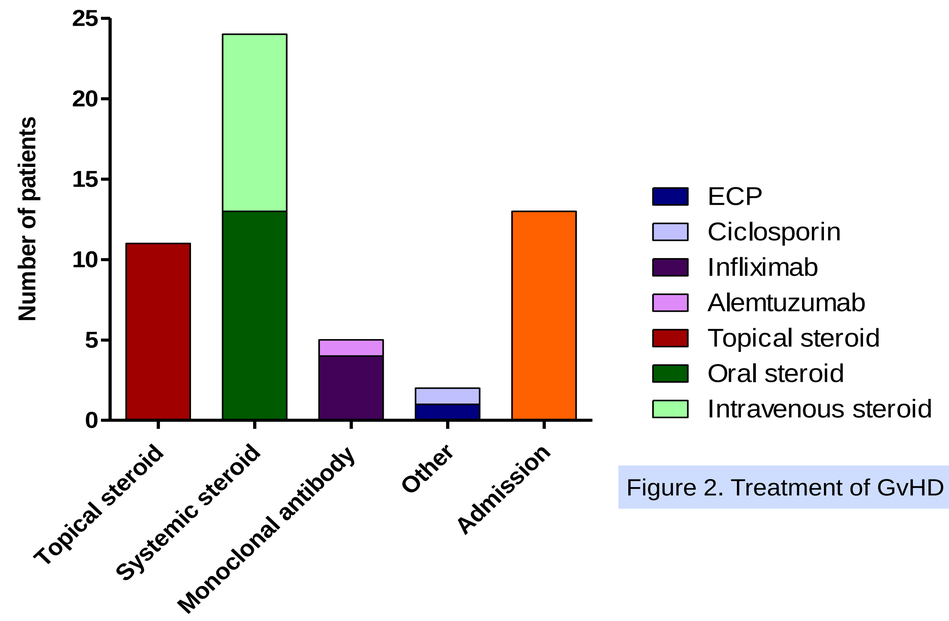

Figure 2. Treatment of GvHD

RESULTS: SURVIVAL

	Survival probability (%)	Standard error	95% CI
100 days	95.9	1.8	92.4-99.5
1 year	82.0	3.6	75.3-89.3
2 years	79.0	3.8	71.8-86.9
5 years	71.1	4.6	62.5-80.8

Table 3. Overall survival

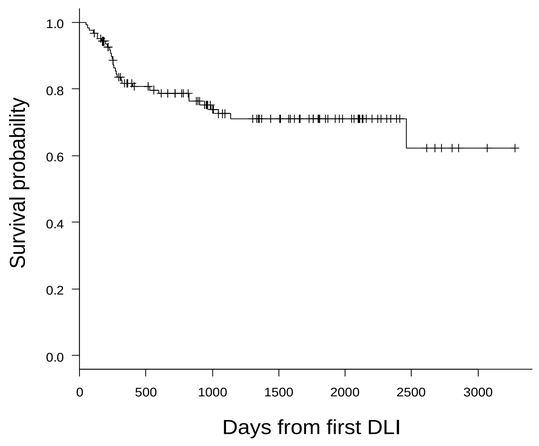

Figure 3. Overall survival

PREDICTORS OF OUTCOME

As time-dependent covariates

Achievement of full donor chimerism predictive of survival (HR 0.28, 95% CI 0.12-0.64, p=0.003)

Severe GvHD predictive of death (HR 6.97, 95% CI 2.76-17.64, p<0.001)

RESULTS: CONVERSION TO FULL DONOR CHIMERISM

72% converted to full donor chimerism (FDC)

Chimerism first measured at median of 112 days

Chimerism measured on average every 37 days post-pDLI until FDC

Median time to FDC was 126 days after 1st pDLI and 92 days after most recent pDLI

Median cumulative pDLI dose to reach FDC: $6x10^6$ CD3+ cells /kg (range $1x10^6$/kg – $2.21x10^8$/kg).

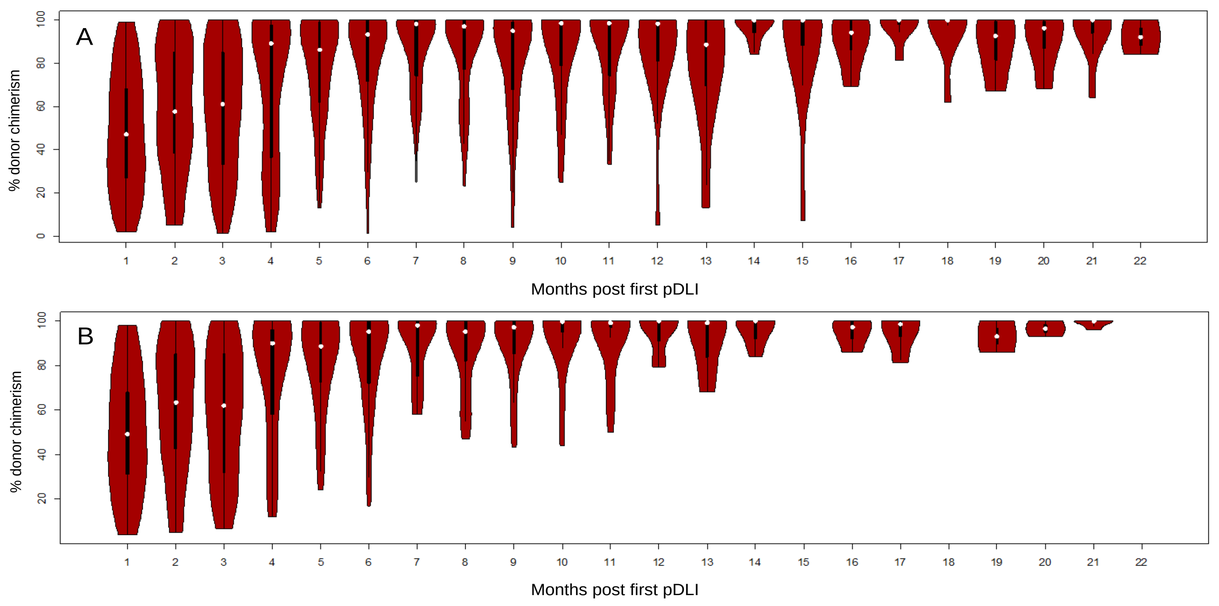

Figure 4. Violin plots of T cell chimerism over time. (A) All pDLI recipients. (B) pDLI recipients who converted to T cell full donor chimerism

Methods

Retrospective case review of consecutive patients between 1st August 2009 and 31st January 2019, who were aged 18 years or over receiving pDLI post allo-SCT for haematological malignancies at the Queen Elizabeth Hospital, Birmingham. Patients were identified from the electronic registry of DLI products issued by National Health Service Blood and Transplant (NHSBT), Birmingham, UK.

The use of DLI was at clinicians' discretion. pDLI is considered when two separate chimerism studies show incomplete donor chimerism in the T cell (CD3+) fraction. Full donor chimerism was defined as ≥98% donor T cell chimerism. At our centre, pDLI is typically given at a starting dose of $1x10^6$ CD3+ cells/kg. Acute GvHD was defined and graded according to the revised Glucksberg criteria,[6] and chronic GVHD according to NIH criteria.[7] Chimerism was assessed by the presence of X or Y chromosomes, or short tandem repeats for sex-mismatched and sex-matched HSCT respectively. This was carried out by the West Midlands Regional Genetics laboratory, Birmingham, UK which is a nationally accredited laboratory.

Tests of significance were two-sided and a p-value less than 0.05 was considered significant. Multivariate survival analyses were carried out using Cox proportional hazard models using backwards elimination of non-significant covariates (p>0.1). Covariates included: age, sex, disease (myeloid *versus* lymphoid), date of transplant (before or after median), days from transplant to first DLI, detectable disease at transplant, related or unrelated donor, donor-recipient sex-mismatch, CMV reactivation, T cell chimerism prior to DLI, and first DLI dose. As only one time-dependent covariate can be included in one model, the effect of GvHD and conversion to FDC on overall survival were included in two separate models.

All patients gave consent at the time of transplant for anonymous data collection on outcomes following allo-SCT for the use in research. Patient identifiable data was held on a password protected computer network at the Queen Elizabeth Hospital. The study had no external funding.

Conclusion

RIC allo-SCT with chimerism monitoring and pDLI for mixed donor chimerism is a safe, effective regimen for patients otherwise unfit for myeloablative conditioning (MAC). In a recent randomised trial of younger patients, RIC allo-HSCT was associated with over 3 times less transplant-related mortality than MAC.[5] RIC allo-SCT with pDLI may therefore be a better strategy than MAC allo-SCT for younger patients which spares toxicity in those patients achieving FDC spontaneously.

Further studies are required to which patients benefit the most from such an approach, and whether pDLI should be offered regardless of chimerism measurement in some cases. The on-going prospective, two-arm, phase II PRO-DLI randomised trial will add valuable further information in this area.[8]

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