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Maintenance therapy for early loss of B-cell aplasia after CD19 CAR T-cell therapy

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Abstract:

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Title

Maintenance therapy for early loss of B-cell aplasia after CD19 CAR T-cell therapy

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To the Editor:

Chimeric antigen receptor (CAR) T-cell therapy has transformed the landscape of relapsed/refractory (r/r) B-cell acute lymphoblastic leukaemia (ALL) in children and young adults,[1,2] with a 3-year relapse free survival of 52% for tisagenlecleucel in the pivotal ELIANA trial.[3] B-cell aplasia (BCA) is an indirect measure of anti-CD19 CAR T-cell presence. Early (≤6 months from infusion) loss of BCA (LBCA) was associated with high relapse risk in studies with tisagenlecleucel or other 41BBz anti-CD19 CAR T products.[4–9] However, with different anti-CD19 CAR T-cells (eg: CD28-containing brexucabtagene), the long-term persistence of CAR T-cells seems not required for durable remission.[10]

The optimal therapeutic strategy for patients with early LBCA after tisagenlecleucel is unclear: good outcomes have been achieved with consolidative hematopoietic stem cell transplant (SCT).[3,9] However, SCT is associated with significant mortality, especially for patients with prior SCT within 12 months,[11] and long term side effects.[12] Indeed, a benefit of consolidative SCT after CAR T was not demonstrated for patients with prior transplant.[13] Moreover, not all patients have a suitable donor and some are precluded from SCT due to co-morbidities. At our centre, children who received tisagenlecleucel and presented early LBCA with a contraindication to SCT were treated with a maintenance chemotherapy regimen for 2 years with promising early outcomes.[14] Here, we report on the longer follow-up of a larger cohort of children and young adults from across the United Kingdom (UK) receiving maintenance chemotherapy or SCT after early LBCA.

We retrospectively collected data on patients treated either with tisagenlecleucel or experimental 41BBz anti-CD19 and anti-CD19/anti-CD22 CAR T-cells (NCT02443831) in the UK from June 2017 until June 2022. The data cut-off date was 20th March 2023. Data were collected on a health service evaluation basis on the basis of outcomes assessment following CAR T cell therapy. Consent for data collection was obtained by patients, parents or legal guardians. Inclusion criteria were early LBCA (≤6 months from infusion) without evidence of disease, defined as morphological complete remission (CR) and negative

minimal residual disease (MRD) by polymerase chain reaction (PCR). LBCA was defined as peripheral B-cell count ≥0.10 x 10^9/L and/or bone marrow CD19+ events ≥0.1%, measured on more than one occasion at least 2 weeks apart. Peripheral lymphocyte subsets were monitored monthly, while marrow aspirate was checked at 1, 3, 6, 9 and 12 months post CAR T-cell infusion. MRD negativity was defined at a lower limit of at least $1x10^{-4}$ by PCR for leukaemia-specific immunoreceptor gene rearrangements. Maintenance was administered as per UKALL2011 protocol (Eudract 2010-020924-22): oral mercaptopurine (75 mg/m^2/daily) with weekly oral methotrexate (20 mg/m^2) and three-monthly intrathecal methotrexate (age-adjusted doses) for 2 years. Patients were also treated with or without monthly pulses (vincristine 1.5 mg/m^2 iv day 1, dexamethasone 6 mg/m^2/day, days 1-5) depending on prior toxicity to these agents. Allogeneic SCT was performed according to institutional guidelines and donor availability.

Categorical variables were compared with two-tailed Fisher's test, continuous variables with the Wilcoxon test for unpaired data. Survival was calculated by Kaplan-Meier analysis and group comparison by Log Rank test. Overall survival (OS) was defined as time from LBCA until death, patients were censored at last follow-up. Event-free survival (EFS) was defined as time from LBCA until death or relapse, whichever occurred first. Significance was set at p value of <0.05 (two-sided).

We retrospectively collected data on paediatric and young adult patients (up to 25 years) treated in the UK for ALL with tisagenlecleucel, AUTO1 or AUTO1/22 (experimental 41BBz anti-CD19 or anti-CD19-CD22 CAR T-cell product, respectively, NCT02443831). Of 151 patients infused (125 tisagenlecleucel, 14 AUTO1, 12 AUTO1/22), 137 (90.7%) (115 tisagenlecleucel, 12 AUTO1, 10 AUTO1/22) achieved CR with onset of BCA and were evaluable up for longer term outcomes. Of these, 32 patients (21.2%) (27 tisagenlecleucel, 3 AUTO1 and 2 AUTO1/22) developed early LBCA with no evidence of detectable disease. In 11/32 (34.3%) allogeneic SCT was undertaken, 8 (25%) were started on maintenance therapy, 6 (18.7%) had no further therapy, 4 (12.5%) received a second tisagenlecleucel infusion, 2 (6.2%) had other treatment, 1 (3%) missing data. Out of the 6 patients that received no immediate treatment for early LBCA, 5 had a frank relapse: 2 are alive in CR, 2 died of disease, 1 died after achieving another remission (Supplementary table).

For the purposes of this report, the study population comprised the 11 patients who received SCT and the 8 patients who received maintenance. These included 17 receiving tisagenlecleucel and 2 receiving experimental CAR T-cell products (1 AUTO1, 1 AUTO1/22). Reasons for being treated with maintenance rather than SCT were: prior total body irradiation (TBI)-based SCT (3 patients), absence of well-matched SCT donor (2), patient co-

morbidities (2) and family preference (1). The baseline characteristics of patients in each treatment cohort were well-matched (Table 1). All patients achieved CR/CRi at day 30 post CAR T and the median time to LBCA was similar in the 2 cohorts. Median follow-up time from LBCA was 21.5 months (95%CI: 12.3,-) for the SCT and 23 months (95%CI: 14.7,-) for the maintenance group. There was no significant difference between the survival of patients receiving either SCT or maintenance: the 1-year OS was 80.8% (95%CI: 60-100) and 75% (95%CI 50.3-100), respectively; 1-year EFS was 80.8% (95%CI 60-100) and 75% (95%CI 50.3-100), respectively ($p>0.05$) (Figure 1). In the transplant group, 2 patients relapsed with CD19-negative disease one and 2 years post-SCT, both are alive receiving further treatment. Two patients died of transplant-related mortality (TRM). Seven patients (63.6%) remain alive in molecular remission without further treatment. In the maintenance group, 3/8 (37.5%) patients relapsed with CD19-positive disease at a median 76 days (95%CI: 60,-) after LBCA: 1 patient was transplanted, had a further relapse and is currently alive with disease; 2 patients died of disease; no patients died of treatment-related toxicity. Five patients (62.5%) remain alive in molecular remission: 2 have completed 2 years of maintenance and 3 remain on maintenance therapy. Of these patients, 4 had favourable cytogenetics (1 ETV6-RUNX1 and 3 high hyperdiploid), 1 had KMT2A rearrangement and 1 had complex cytogenetics.

Early LBCA after tisagenlecleucel is associated with a high risk of relapse: cumulative incidence of CD19+ relapse approached 65% at 2 years in a French cohort,[7] while the 2-year EFS was 15% for patients with LBCA <6 months in a recent study.[5] Treatment strategies for this group remain limited. Infusion of a further dose of the same CAR T-cell product re-induced BCA in approximately half of patients without detectable disease, but the 3-year disease-free survival (DFS) was only 33%.[15] Most patients have been treated with SCT in this context. A study from the National Instititute of Health reported a 5-year EFS of 61.9% in 21 patients who received consolidative SCT after non-persisting anti-CD19-CD28z CAR T-cells.[9] However, whether SCT confers a definitive survival advantage in this setting is as yet unclear. A Seattle group reported that SCT led to improved DFS among 23 patients with short persistence of experimental anti-CD19 41BBz CAR T; however, this did not translate into a better OS and the benefit of consolidative SCT was only seen in patients without a prior history of SCT.[13]

In a single-centre setting, we noted good outcomes from maintenance therapy in preliminary patients with a contra-indication to SCT.[14] As a UK pediatric ALL CAR T consortium, we therefore collected data on patients with early LBCA to compare the impact of maintenance versus SCT. Our analysis shows that maintenance was a safe alternative for these patients. Despite a slightly higher number of relapses in the maintenance group, there were no TRM

events in this group, compared to 2 TRM deaths following SCT. As a result, both groups had similar OS and EFS. This highlights the toxicity of SCT in heavily pre-treated patients.

Maintenance was well-tolerated, low-cost, easy to deliver, with a good quality of life reported informally by patients and their families. Due to the small size of the cohort, it was not possible to identify predictive factors for patients with a good outcome from maintenance, e.g. characteristics suggesting particularly chemosensitive disease, however 4 out of 6 patients had good risk cytogenetics at diagnosis.

Our preliminary study is limited by the retrospective design and, despite being population-based, by the small cohort size; moreover, we recognise that longer term follow-up will be needed to capture late relapses seen in some genetic subtypes e.g. ETV6-RUNX1 and high hyperdiploid ALL.

Our data show that maintenance chemotherapy could have a potential benefit in patients with LBCA who cannot proceed to SCT or second CAR T infusion, either because of contraindications, or because of limited resources. A prospective clinical trial comparing SCT versus maintenance is needed to clearly define outcomes of these therapies in this setting.

Authorship

M.G., M. O-E, P.A. and S.G designed the research study and wrote the manuscript, M.G and M. O-E. collected and analyzed the data; all authors looked after patients, provided essential data, reviewed and approved the final manuscript.

Disclosure of interests

P.J.A.: *UCL Business:* Patents & Royalties; *Autolus:* Patents & Royalties, Research Funding; *Beam therapeutics*: Consultancy

S.G:*Novartis:* Honoraria, Speakers fees; *UCLB:* Patents & Royalties.

All other authors report no conflict of interests.

Data availability statement

The datasets are available from the corresponding author on reasonable request: s.ghorashian@ucl.ac.uk.

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Table I

Characteristic of patients, disease and treatment.

Abbreviations:

n number, IQR interquantile range, pts patients, CAR chimeric antigen receptor, WCC white cell count, NCI national cancer institute, CNS central nervous system, EM extra-medullary, SCT stem cell transplantation, MRD minimal residual disease, LBCA loss of B-cell aplasia, TBI total body irradiation, MUD matched unrelated donor, MMUD mismatched unrelated donor, UCB umbilical cord blood, MSD matched sibling donor, Haplo haploidentical, VCR vincristine, Dexa dexamethasone

Variable	n=19 WHOLE TREATED COHORT		n=11 ALLO-SCT		n=8 MAINTENANCE		P
	n or median	% or IQR	n or median	% or IQR	n or median	% or IQR	
Male	6	31.60%	3	27.30%	3	37.5%	1
Age at CAR T-cell infusion	7.9 years	6.1-12.6	7.9	6.3-12.8	8.75	4.9-12.2	0.8043
Characteristics of initial diagnosis							
Age 0-1 years (n of pts)	3	15.80%	1	9.10%	2	25%	0.5459
Median WCC	10	9.4-99.8	10	9.9-44	40	8.5-128.5	0.8729
NCI risk							
High	7	36.80%	2	27.30%	4	50%	0.37
Standard	9	47.40%	7	54.50%	3	37.50%	
Not known	3	15.80%	2	18.20%	1	12.50%	
Cytogenetic risk							
Good risk	**9**	**47.40%**	**5**	**45.50%**	**4**	**50%**	
ETV6-RUNX1	3	15.80%	2	18.20%	1	12.50%	
High hyperdiploid	6	31.60%	3	27.30%	3	37.50%	
Intermediate risk	**1**	**5.30%**	**1**	**9.10%**	**0**		
IKZF1 deletion	1	5.30%	1	9.10%	0		
High risk	**5**	**26.30%**	**3**	**27.30%**	**2**	**25%**	
KMT2Ar	3	15.80%	1	9.10%	2	25%	1
BCR-ABL	1	5.30%	1	9.10%	0		
t(17;19)/ TCF3-HLF	1	5.30%	1	9.10%	0		
Uninformative cytogenetics*	**4**	**21.10%**	**2**	**18.20%**	**2**	**25%**	
Unknown	1	5.30%	1	9.10%	0		
Other	3	15.80%	1	9.10%	2	25%	
Characteristics of relapsed/refractory disease							
Indication for CAR T							
Primary refractory	1	5.30%	1	9.10%	0		1
After relapse	18	94.70%	10	90.90%	8	100%	
Refractory status							
At any time point	11	57.90%	7	63.60%	4	50%	0.6577
N° of relapses	1	1.0-2.0	1	1.0-1.5	1.5	1.0-2.0	0.2754
CNS and extramedullary disease							
CNS at any point	11	57.90%	5	45.50%	6	75%	0.3521
EM non-CNS relapses (both isolated and combined)	2	10.50%	1	9.10%	1	12.50%	1

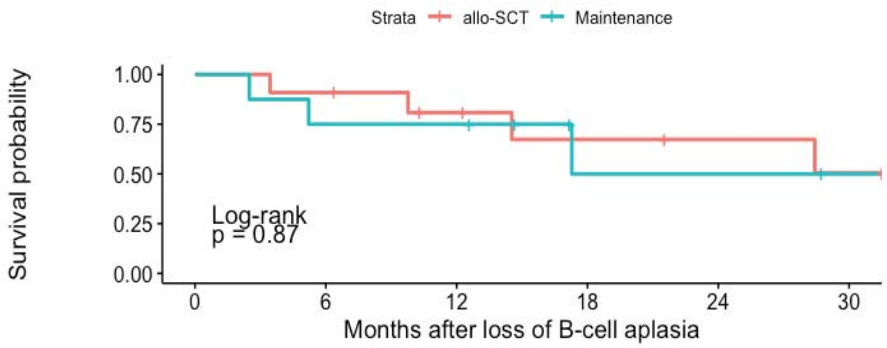
N° of previous therapy lines (excluding SCT)	2	2.0-2.0	2	2.0-2.0	2	2.0-2.2	0.7737
Prior SCT	5	26.30%	2	18.20%	3	37.50%	0.6027
Blinatumomab exposure	4	21.10%	1	9.10%	3	37.50%	0.2621
Inotuzumab exposure	1	5.30%	0		1	12.50%	0.4211
CAR T -cell therapy							
Status pre-lymphodepletion							
High disease burden (>=5%)	3	15.80%	2	18.20%	1	12.50%	1
Low disease burden (<5%)	11	57.90%	6	54.60%	5	62.50%	
Undetectable by MRD	5	26.30%	3	27.30%	2	25%	
CAR T-cell product							
Tisagenlecleucel	17	89.50%	10	90.90%	7	87.50%	1
Experimental	2	10.50%	1	9.10%	1	12.50%	
Median CAR T-cell dose/kg (n= 17)	2.7E+06/kg	1.8-3.7	3.4E+06/kg	2.5-4.3	2.4E+06/kg	1.5-2.8	0.2069
Time to LBCA							
median	2.66 months	2.3-3.6	2.66	2.07,-	2.64	2.3,-	0.9
0-3 months	13	68.4%	7	63.60%	6	75%	1
3-6 months	6	31.60%	4	34.4%	2	25%	
Post CAR T-cell treatment							
Median time from LBCA to SCT	2.4 months	1.7 – 4.5	1				
SCT conditioning							
TBI-based			8	72.7%			
Non TBI			3	27.30%			
SCT Donor							
MUD			7	72.70%			
MMUD (UCB)			1	9.00%			
MSD			2	18.20%			
Haplo			1	9.00%			
Maintenance with VCR/Dexa pulses							
Yes					4	50%	
No					4	50%	

255

256

Figure 1: Event-free survival (A) and overall survival (B) for patients treated with allogeneic stem cell transplantation (red line) or maintenance (green line) after early loss of B-cell aplasia post CAR T-cell treatment.

A)



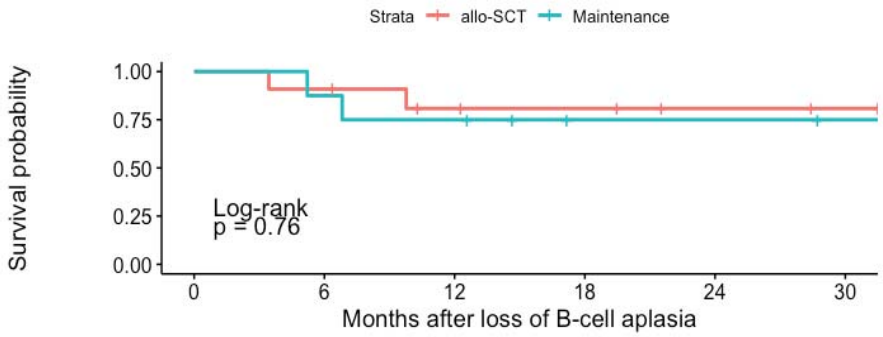
Number at risk

allo-SCT	11	10	7	5	4	3
Maintenance	8	6	6	2	2	1

Cumulative number of events

allo-SCT	0	1	2	3	3	4
Maintenance	0	2	2	3	3	3

B)



Number at risk

allo-SCT	11	10	7	6	4	3
Maintenance	8	7	6	3	3	2

Cumulative number of events

allo-SCT	0	1	2	2	2	2
Maintenance	0	1	2	2	2	2