CAR T therapy for relapsed/refractory large B-cell lymphoma in people living with HIV: efficacy, toxicity and treatment considerations

Despite highly effective combination anti-retroviral therapy (aRT), people living with human immunodeficiency viruses (HIV) (PLWH) remain at increased risk of non-Hodgkin lymphoma (NHL). Large B-cell Lymphoma (LBCL) is the commonest subtype[1] (including immunoblastic and anaplastic morphological variants) and classically presents in advanced stage with extranodal involvement.[2] Mechanistically, HIV contributes to lymphomagenesis through loss of immune surveillance via HIV-dependent CD4$^+$ T-cell depletion, direct viral oncogenesis, and Epstein Barr virus-driven aberrant B-cell proliferation.[1,2]

Whilst outcomes have improved in the first line following standard-of-care therapy (R-CHOP;[3,4] R-EPOCH[5]), LBCL remains a leading cause of mortality in PLWH, and management of relapse remains a major challenge.[2]

Chimeric antigen receptor T-cell therapy (CAR T) has transformed outcomes in relapsed/refractory (r/r) LBCL, with 40-50% of patients achieving durable complete responses (CR).[6] Several small case series indicate that commercial CAR T for HIV-associated LBCL is feasible,[7-10] albeit data on safety and efficacy is limited, as PLWH with LBCL were excluded from pivotal trials. Here we report the UK experience of commercially available CD19 CAR T therapy, specifically axicabtagene ciloleucel (axi-cel), for HIV-associated LBCL in the second and third line, with a focus on feasibility, toxicity and efficacy.

Eleven UK patients with HIV-associated LBCL were referred for CAR T therapy between 2019-2025: four of 11 (36%) at second line and seven of 11 (64%) at third/later line, with eligibility criteria the same as for non-HIV-associated LBCL. An additional patient who self-funded treatment was also included. Ethical approval was obtained (REC-reference:24/EM/0221;IRAS project-ID:336254) and the study was conducted in accordance with the Declaration of Helsinki. Patients provided informed consent for collection of minimally identifiable data in line with European Society for Blood and Marrow Transplantation policy.

The median interval from HIV diagnosis to LBCL diagnosis was 16 years (range, 0-31) and all cases were histologically LBCL. At LBCL diagnosis, median CD4 count was 65 cells/μL (range, not detected [ND]-182) and HIV viral load was <40 copies/mL (range, ND-6,840,000). First-line treatment included R-CHOP in seven of 11 (64%), R-Pola-CHP in two of 11 (18%) and R-GCVP in two of 11 (18%). Only three of 11 (27%) achieved a response with one CR and two partial responses (PR) and progressive disease (PD) in eight of 11 (73%). At CAR T referral, patients had received a median of two prior lines (range, 1-3) including autologous stem cell transplant (ASCT) in only one patient (9%). HIV and LBCL diagnostic details are summarized in *Online Supplementary Table S1*.

Patient and disease characteristics are summarized in Table 1. At CAR T referral, median age was 55 (range, 32-74), nine of 11 patients were male, nine of 11 had stage III/IV disease and ten of 11 had extranodal involvement. No patients had central nervous system (CNS) involvement.

All referred patients underwent apheresis and CAR T manufacture (median lymphocyte count 1.84x10^9/L [range, 0.42-3.23]; median CD4$^+$ count 186 cells/μL [range, 70-410]). Most CAR T products met release criteria (10/11; 91%) with only one failure from low transduction efficiency which was ultimately approved by the UK out of specification (OOS) panel due to clinical need, and the Summary of Product Characteristics (SmPC) defined CAR$^+$ viable cell dose was infused.

All patients received bridging therapy (BT): eight of 11 (73%) received systemic BT (including polatuzumab-based BT in 6/8 patients); two of 11 (18%) received radiotherapy only; and one of 11 (9%) received combined systemic and radiation BT. CR/PR responses were infrequent (3/11 patients), with PD reported in all other patients. Three patients (27%) did not proceed to CAR T. This was due to PD in two patients (including 1 with new CNS involvement) and clinician preference in one patient who achieved CR to BT but swiftly relapsed thereafter with rapid clinical deterioration. Eight of 11 (73%) patients proceeded to CAR T infusion (including 1 patient with an OOS product), and median pre-lymphodepletion (LD) lactate dehydrogenase (LDH) and ferritin were 324 (range, 145-549) and 761 (range, 128-2,832) respectively.

Toxicity is summarized in Table 2. Briefly, any grade (G) CRS or immune effector cell-associated neurotoxicity syndrome (ICANS) affected seven of eight (88%) and three of eight (38%) patients respectively. Grade ≥3 CRS and ICANS affected one of eight (13%) and two of eight (25%) patients. Grade ≥3 infection affected two of eight patients (25%). High-grade immunotoxicity (plus concomitant sepsis and PD in 1 patient) prompted intensive care unit admission in three of eight patients (34%) with two of three requiring inotropes and one of three requiring ventilatory support. No patients developed HIV viremia immediately post-CAR T. Whilst no overt signal for protracted ≥G3 neutropenia or thrombocytopenia was reported, the dataset is limited by small patient numbers in remission beyond months 1-2. In

Table 1. Baseline characteristics, bridging therapy and month 1 outcomes.

Baseline characteristics	All patients N=11	Infused N=8
Age at approval, years, median (IQR)	55 (47-60)	53.5 (47-59)
Range	32-74	32-62
Sex, N (%)		
Male	9 (82)	6 (75)
Female	2 (18)	2 (25)
Disease stage, N (%)		
I	1 (9)	1(13)
II	1 (9)	1(13)
III	2 (18)	1 (13)
IV	7 (64)	5 (63)
Extranodal involvement, N (%)		
No	1 (9)	0
Yes	10 (91)	8 (100)
Lymphocyte count, x10⁹/L at apheresis, median (IQR)	1.84 (1.2-2.7)	2.1 (0.9-2.9)
Range	0.42-3.23	0.42-3.23
CD4⁺ count, cells/μL at apheresis, median (IQR)	186 (130-315)	202 (90-363)
Range	70-410	70-410
Out of specification product, N (%)		
No	10 (91)	7 (88)
Yes	1 (9)	1 (13)
Bridging therapy, N (%)		
Systemic	8 (73)	5 (63)
RBP	3	2
R-polatuzumab	3	1
R-gemox	1	1
R-ICE	1	1
Radiotherapy	2 (18)	2 (25)
Combined modality (RT + R-polatuzumab)	1 (9)	1 (13)
Response to bridging by PET-CT,§ N (%)		
CR	2 (18)	1 (13)
PR	1 (9)	1 (13)
PD	8 (72)	6 (75)
Combined aRT therapy,** N (%)		
Bictegravir/emtricitabine/tenofovir alafenamide	3 (27)	3 (38)
Emtricitabine/tenofovir alafenamide + nevirapine	2 (18)	1 (13)
Emtricitabine/tenofovir alafenamide + raltegravir	1 (9)	1 (13)
Emtricitabine/tenofovir alafenamide + dolutegravir	1 (9)	-
Emtricitabine/tenofovir alafenamide + dolutegravir + fostemsavir	1 (9)	1 (13)
Emtricitabine/tenofovir disoproxil fumarate + raltegravir	1 (9)	-
Missing	2 (18)	2 (25)
Pre-lymphodepletion*		
LDH pre-LD, median (IQR)		324 (202-426)
Range		145-594
Ferritin pre-LD, median (IQR)		761 (185 -1,290)
Range		128-2,832
CRP pre-LD, median (IQR)		7 (6-32.9)
Range		3.2-48.7
PS pre-LD, N (%)		
0	-	2 (25)
1		4 (50)
2		2 (25)
HIV viral load, pre-LD, N (%)		
Not detectable		6 (75)
Detected		0 (0)
Missing/not assessed		2 (25)
CD4⁺ count, cells/μL		
Baseline pre-LD, median (IQR)		196 (130-290)
Range		108-410

Continued on following page.

Baseline characteristics	All patients N=11	Infused N=8
M1 post CAR T		
CD4⁺ count, cells/μL		
Result		39, 40, 80, 249
Missing, N	-	4
M1 response by PET-CT,§ N (%)		
CR		2 (25)
PD		4 (75)

*Lymphodepletion (LD) comprised fludarabine and cyclophosphamide as per summary of product characteristics. **Combined anti-retroviral therapy (aRT) regimens were at the discretion of local investigators with human immunodeficiency virus (HIV)-specialist teams. §Positron emission tomography-computerised tomography (PET-CT) response was according to Lugano 2014 classification at month 1 (M1) and month 3 (M3) following infusion. CAR T: chimeric antigen receptor T-cell; CR: complete response; CRP: C-reactive protein; IQR: interquartile range; LD: lymphodepletion; LDH: lactate dehydrogenase; RBP: rituximab, bendamustine, polatuzumab; R-gemox: rituximab, gemcitabine, oxaliplatin; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; R-polatuzumab: rituximab, polatuzumab; PD: progressive disease; PR: partial response; PS: performance status.

regard to immune reconstitution, at 12 months post-CAR T, the two long-term responders have lower CD4⁺ counts than at the time of leukapheresis i.e., from baseline 170 and 410 cells/μL, to 90 and 270 cells/μL at 12 months.

Response data is summarized in Figure 1A. The overall response rate (ORR) at the first month (M1) was 25% (2/8 patients), with CR ongoing in the two responding patients at 12 and 20 months of follow-up. PD was reported at M1 in six of eight patients (75%). Notably, no patients with a PD response to BT achieved a response to CAR T infusion (Figure 1A).

Figure 1B shows OS for the intention-to-treat (ITT) population (N=11). For infused patients (N=8), Figure 1C shows a median OS from infusion of 10.8 months (interquartile range, 1.7-11.8) and Figure 1D shows a median progression free survival (PFS) from infusion of 0.9 months (IQR, 0.8-1.7). Six of eight (75%) patients developed PD post-CAR T. Two of six (33%) received R-CHOP salvage followed by Glofitamab to PD, and one of six patients (17%) received Glofitamab salvage to PD. Three of six patients (50%) were transferred to palliative care without further therapy. Only one of six patients with PD post-CAR T is alive at 3 months post-PD.

Whilst CAR T therapy has revolutionized non-HIV-associated LBCL, a paucity of data in PLWH reflects exclusion of these patients from clinical trials, albeit real-world data is beginning to emerge.[9,10] Here we report our experience using CD19 CAR T in 11 PLWH with r/r LBCL. Clinical outcomes were disappointing, with only eight of 11 patients reaching CAR T infusion. Further, the post-CAR T ORR was only 25%, with extremely short PFS and OS compared to non-HIV LBCL CAR T patients.[11] Evaluating baseline demographics, it is clear that our cohort was enriched for patients at high risk of CAR T failure, namely those with high disease burden (including high LDH pre-LD), those with extranodal disease[12] and those with primary refractory disease, most of whom did not respond to BT. Learning from the two patients who achieved durable CR on our study, both were distinguished from other patients in the analysis by having achieved disease control post-BT and by having limited-stage disease (1E and IIE).

Other published analyses of CAR T for B-NHL in HIV includes a conference abstract from the collaborative CIBMTR and AIDS Malignancy Consortium (AMC) study which included 35 PLWH and reported 1 and 2 year OS rates of 45.7% and

Table 2. Toxicity.

Toxicity	Infused N=8
CRS, N (%)	
Any grade	7 (88)
Grade ≥3	1 (13)
ICANS, N (%)	
Any grade	3 (38)
Grade ≥3	2 (25)
ICU admission, N (%)	
No	5 (63)
Yes	3 (38)
Immunotoxicity	2
Infection/sepsis and immunotoxicity	1
Grade 3-4 neutropenia M1,* N (%)	
No	2 (100)
Yes	0
Grade 3-4 thrombocytopenia M1,* N (%)	
No	2 (100)
Yes	0
Grade 3-4 neutropenia M3,* N (%)	
No	2 (100)
Yes	0
Grade 3-4 thrombocytopenia M3,* N (%)	
No	2 (100)
Yes	0
Grade 3-4 infection,* N (%)	
No	6 (75)
Yes	2 (25)

*For 1- and 3-month (M1 and M3) cytopenia; patients with progressive disease at M1 or M3 have been excluded. CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICU: intensive care unit.

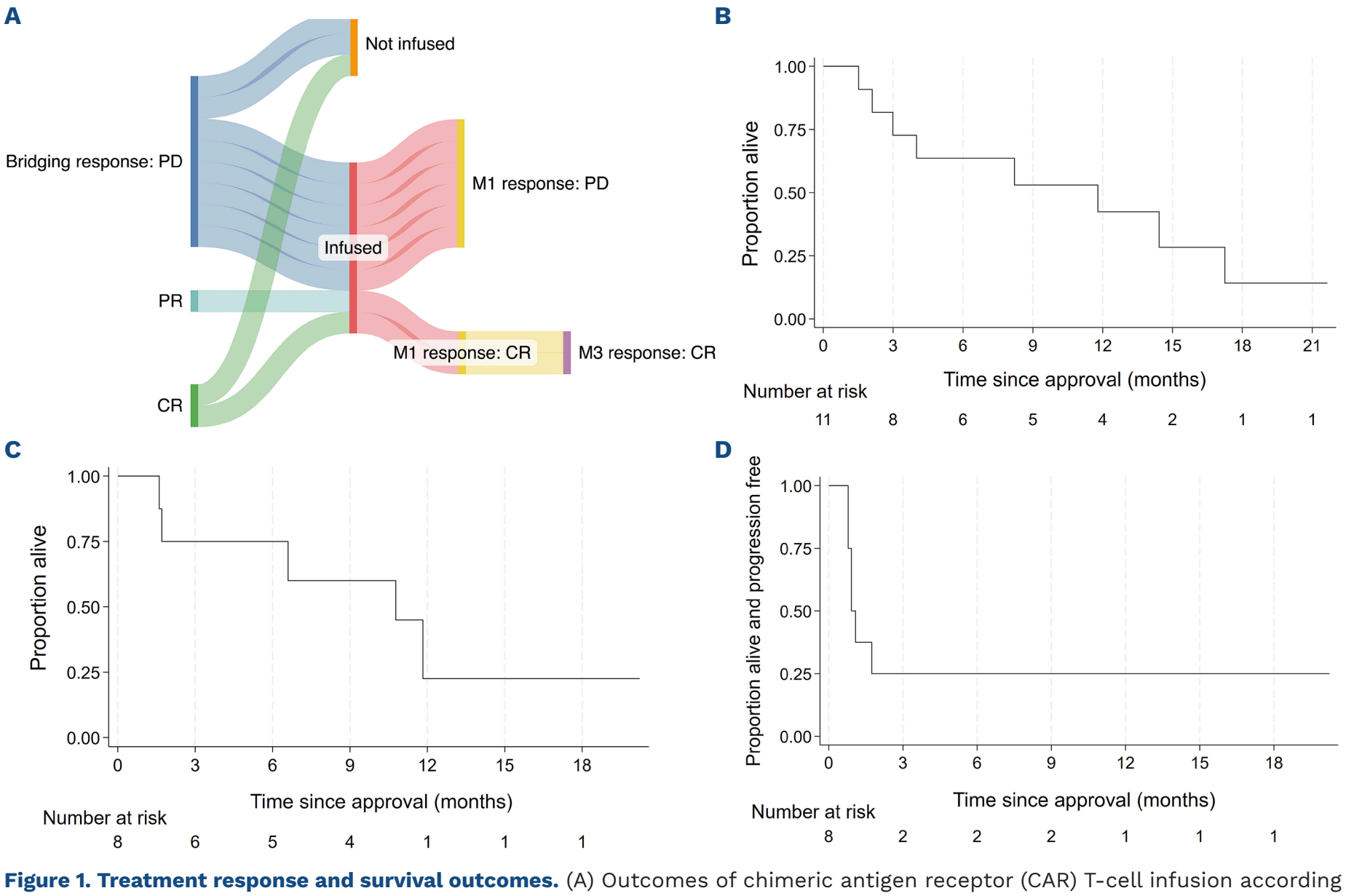

Figure 1. Treatment response and survival outcomes. (A) Outcomes of chimeric antigen receptor (CAR) T-cell infusion according to bridging response. (B) Overall survival (OS) from approval. Median OS 11.8 months (interquartile range [IQR], 3.0-17.2). (C) OS from infusion. Median OS 10.8 months (IQR, 1.7-11.8). (D) Overall progression-free survival (PFS) from infusion. Median PFS 0.9 months (IQR, 0.8-1.7). PD: progressive disease; PR: partial response; CR: complete response; M1: month 1; M3: month 3.

65.9% respectively.[13] In a separate conference abstract from the DESCAR-T group of axi-cel for B-NHL in 24 PLWH (20/24 with LBCL), Clerico *et al*. report an impressive M3 ORR of 50%, CR rate of 42% and a 12-month PFS and OS of 40% and 55%.[7] All grade CRS and ICANS affected 88% and 33% of patients, similar to what is observed with axi-cel in the non-HIV setting.[11] A comparison of our dataset to these studies is summarized in *Online Supplementary Table S2*.

Whilst these outcomes appear better than our UK outcomes, there are several factors which may explain the discrepancy. Firstly, the DESCAR-T cohort was heterogenous in disease type, including cases of follicular and grey zone lymphoma. Secondly, treatment history suggests less aggressive/refractory disease compared to the UK cohort, in that 17% of patients had prior ASCT (*vs*. 9% in the UK cohort). Further, only 63% required BT (*vs*. 100% in the UK cohort), of whom 26% received radiotherapy/steroids which again implies limited stage disease. These knowledge gaps make it difficult to determine the true potential of CAR T for HIV-associated lymphoma, and further clinical data is urgently required to delineate prognostic risk factors and optimal approaches to bridging in this challenging clinical setting.

From a practical perspective, there are several unique considerations when delivering CAR T in PLWH. Firstly, HIV viral load should be well controlled pre-CAR T to facilitate CAR T manufacture, favoring successful T-cell harvest (as a result of optimized immune reconstitution), and minimizing the theoretical risk of vector recombination with native HIV virus.[9,14] In line with FACT-JACIE standards,[15] products require segregated storage at site or transportation to site on the day of infusion to minimize infectious risk in shared storage. Patient management requires close multi-disciplinary working between hematology and HIV specialist teams for awareness of aRT/drug interactions, and optimal infection prophylaxis. Our study showed good HIV control pre-LD and post-CAR T infusion was feasible, with no cases of viral rebound.

In summary, our study illustrates the UK real-world experience of CD19 CAR T for HIV-associated LBCL in second and later lines. Whilst definitive conclusions are limited by the retrospective nature of the analysis, the heterogeneity of BT, and the small patient numbers, our analysis clearly highlights the challenges of CAR T treatment delivery in PLWH, where high-risk LBCL disease phenotypes (namely primary refractory/elevated LDH/high stage/extranodal disease) may

help explain the poor outcomes we report here. Overall, patients with limited-stage and low-burden disease may have better outcomes, but more work is needed to understand which patients will benefit most from CD19 CAR T. Prospective clinical trials will be crucial in defining the role for CAR T in PLWH, towards efforts to improve outcomes in this patient group.

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Disclosures

AAK has received honoraria from Kite/Gilead, Janssen, and BeOne Medicines. MOR has served on advisory boards and received honoraria from Kite/Gilead, Novartis, and Janssen. AK has served on advisory boards and received honoraria from Kite/Gilead, Novartis, Abbvie, Roche, and Bristol Myers Squibb. MN has received honoraria from Kite/Gilead. PM holds patents with UCL Business, holds equity in Autolus and has received research funding from Autolus. SC has served on advisory boards and/or received honoraria from Kite/Gilead, Roche, Abbvie, Pierre Fabre, Bristol Myers Squibb, Autolus, Takeda, Incyte, and Roche. KC has served on advisory boards and/or received honoraria from Kite/Gilead, Roche, Incyte, Abbvie, Bristol Myers Squibb, Secura Bio, Autolus, Sobi, Takeda, Atara, Janssen, and Acrotech. RS has served on advisory boards and/or received honoraria from Abbvie, Astra Zeneca, Bristol Myers Squibb, Johnson & Johnson, and Kite/Gilead. CR has served on advisory boards and/or received honoraria from Kite/Gilead, Novartis, Autolus, Johnson&Johnson, Bristol Myers Squibb, Cellistic, and Kyverna. The remaining authors have no conflicts of interest to disclose.

Contributions

AH, AAK, and CR designed the project. AH, MOR, RS, PH, MA, and MN compiled the clinical data. AH, AAK, MOR, and CR wrote the manuscript. All authors edited and reviewed the manuscript.

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Data-sharing statement

De-identified data that support the findings of this study are available on request from the corresponding author.

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