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LETTER TO THE EDITOR

Management of immunosuppression in post-transplant lymphoproliferative disorders treated with CAR T cells

Post-transplant lymphoproliferative disorders (PTLD) represent a continuum of lymphoid neoplasms arising after solid organ (SOT) or haematopoietic stem cell (HSCT) transplantation.[1] Histologically, PTLD are a heterogeneous group,[2,3] sharing similarities with diffuse large B-cell lymphoma (DLBCL). Rituximab, with or without chemotherapy, is the current standard-of-care, often yielding long-term remission.[4,5] Yet, relapses are of poor prognosis.[5] Chimeric antigen receptor (CAR) T-cell therapy (CAR-T), remarkably efficient in refractory/relapsed (R/R) DLBCL,[6] could be a therapeutic option for PTLD, the major issue being the management of anti-rejection treatment in such cases.[5] Here, we report the case of a PTLD patient treated with CAR-T, review similar cases and discuss immunosuppression (IS) management in these patients.

A 24-year-old EBV-negative woman, with bilateral renal cortical necrosis due to *Neisseria meningitidis* W135 infection and purpura fulminans, received an EBV-positive kidney transplant in August 2022. Five months later, a left latero-cervical lymphadenopathy developed and was biopsied, disclosing a DLBCL-like monomorphic PTLD with 80% Ki67 proliferation index and positive in situ hybridization for EBV-encoded RNA (EBER). The plasma EBV viral load was 3.79 log/IU/mL. Positron emission tomography/computed tomography (PET/CT) detected several lesions (Figure S1). LDH levels were normal, and the revised international prognostic index score was 2.

At PTLD diagnosis, IS (mycophenolate mofetil [MMF], tacrolimus and prednisone) was reduced by discontinuing MMF. Weekly rituximab monotherapy (375 mg/m^2) was initiated and intensified to R-CHOP after 2 weeks because of tumour progression. PET/CT after one R-CHOP cycle showed progression of the cervical mass, with new lung and liver involvement. Cervical radiotherapy (36Gy) provided little improvement (Figure S1). EBV-directed/HLA-compatible cytotoxic T-lymphocytes being unavailable, CAR-T were indicated. Prednisone was reduced (10 mg/d), and tacrolimus switched to everolimus, which was suspended 5 days before leukapheresis. Bridging included two cycles of rituximab, gemcitabine and oxaliplatin, leading to stable disease (Figure S1). IS was totally discontinued a week before lymphodepletion. The latter comprised a 3-day fludarabine (30 mg/m^2/d) and cyclophosphamide (500 mg/m^2/d) regimen. Axicabtagene ciloleucel (axi-cel) was infused in May 2023, yielding a spontaneously resolutive grade-1 cytokine-release syndrome (CRS). No immune-effector cell-associated neurotoxicity syndrome (ICANS) was observed. PET/CT showed stable disease at 1 month (M1, Figure S1) and complete remission (CR) at M2 (Figure S1), sustained at M6. Figure 1 shows the biological evolution of flow cytometry-assessed peripheral CAR-Ts, EBV viral load and circulating tumour DNA (ctDNA). The latter and the lymphoma-specific clonotype were tracked in liquid biopsies (Supplemental material). The renal function remained stable. Donor-specific anti-HLA antibodies (DSA) and donor-derived cell-free DNA (dd-cfDNA), monitored monthly, were negative throughout. Corticosteroid-based IS was resumed at M5 (prednisone 10 mg/d) and full IS at M6 (tacrolimus 1 mg/d). The patient remained free of IS for 6 months without any biological sign of graft rejection (Figure S1).

A PubMed search retrieved 48 patients (Table 1; Table S1) with R/R PTLD treated with CAR-T (95.9% DLBCL). Age at diagnosis ranged between 2 and 76 years. The EBV status was essentially negative (69.4%). Most SOT (67.3%) were kidneys. Time between transplant and PTLD ranged between 1.3 and 216 months. CAR-T were axi-cel (63.3%), tisagenlecleucel (20.4%), lisocabtagene maraleucel (4%), brexucabtagene autoleucel (2.1%) and not specified in five cases (2 anti-CD19 and anti-CD22 CAR-T).

CRS (79.6%) was the most common side effect, mostly low grade (3–4 8.2%). ICANS (55.1%) were of grade 3–4 in 48.1%. Post-CAR-T infections (14%) were mainly bacteraemia.

The overall response rate (ORR) was 67.3%, including CR (59.2%), PR (8.2%), stable (10.2%) and progressive (22.4%) diseases. Reported progression-free survival ranged between 0 and 36 months. Twelve patients died, 10 of lymphoma among whom six were 'on' IS at that time.

IS was completely discontinued for leukapheresis in 51% of the patients, while 22% remained on corticosteroids and 27% on IS. At the time of the CAR-T infusion, IS was discontinued for 48.9% of the patients. IS was resumed for 16 after a median of 3 months (1–14). At last follow-up, of 29 patients in CR, nine remained 'off' IS, five continued corticosteroids and 15 were on IS.

Five transplant rejections occurred (kidney $n=4$, liver $n=1$, 10%) at M1 ($n=1$), M4 ($n=2$) and M15 ($n=2$)

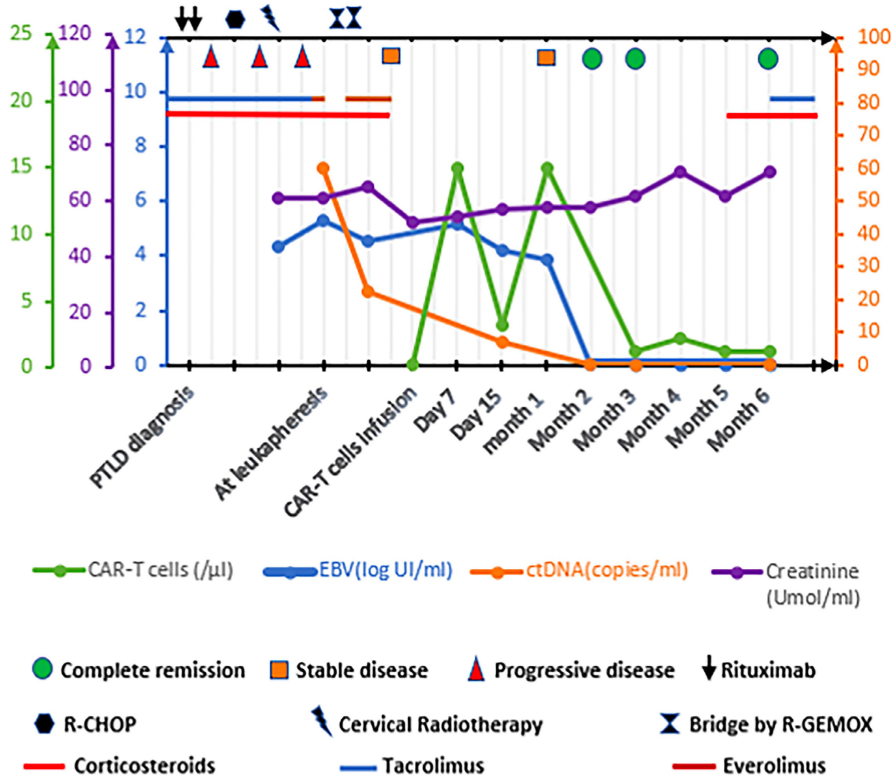

FIGURE 1 Management of immunosuppressive treatment, biomarkers and tumour response in the reported case. CAR-T showed two peaks at Day 7 and Month 1, then remained detectable up to 6 months. The EBV viral load decreased 2 weeks after infusion and became negative at M2. Tumour ctDNA was detected at 750 copies/mL at leukapheresis, dropped after bridging (288 copies/mL), became negative at M2 and remained undetectable at M6. Creatinin levels remained stable, indicating the absence of renal impact of the treatment.

post-CAR-T, despite three patients being on IS at that time. One died of progression (1.5 months postinfusion); the four others were still alive at the data cut-off, two having resumed haemodialysis.

From this focused literature analysis, the efficacy of CAR-T in PTLD (67.3%/59.2% ORR/CR) appears similar to that reported after axi-cel[7] (82%/54%), tisa-cel[8] (52/40%) or liso-cel[9] (73%/53%). Grade 3/4 CRS (8.2%) are close to those of ZUMA-1 (13%),[7] probably because axi-cel was mostly used. More severe ICANS were observed in PTLD (48.1% vs. 28%, 12% and 10% with axi-cel, tisa-cel and liso-cel). The non-relapse-mortality rate (6.1%) seems similar to DLBCL real-world data.[10]

Optimal management of IS during CAR-T therapy for PTLD remains a challenge to preserve CAR-T efficacy while preventing graft rejection. The latter occurred only in five patients (8%) despite frequent and sometimes prolonged IS reduction or discontinuation. Indeed, CAR-T therapy itself induces both cellular and humoral IS through lymphodepletion and CAR-T-induced B-cell aplasia/hypogammaglobulinaemia.[11] To date, however, no consensus endorses the management of IS after CAR-T. For almost half of the patients, IS was discontinued before leukapheresis. IS with low-dose prednisone could be maintained at all times,[12] in line with this review, where nearly 60% of the patients received only low-dose corticosteroids prior to CAR-T. This is also supported by the ZUMA-1 post hoc analysis,[13] suggesting that early corticosteroid treatment did not influence peripheral CAR-T peak levels nor response.

Although response rates seem comparable to those of immunocompetent patients, response duration after CAR-T for PTLD may be shortened by the need to resume IS, suggesting that IS should remain suspended as long as possible. This decision-making process is of an inherently personalized nature. In our patient, response was closely monitored with ctDNA and graft rejection with DSA and dd-cfDNA to continuously assess the risk/benefit of IS suspension.

Overall, this analysis confirms that CAR-T therapy is feasible and effective in PTLD, yet without consensus regarding IS management. Prolonged cellular and humoral IS, provided by lymphodepletion and CAR-T infusion, respectively, allows for an acceptable transient reduction or discontinuation of IS. Careful monitoring of immune reconstitution, signals of graft rejection and post-CAR-T tumour response is crucial to tailor IS in a personalized and dynamic manner, with close coordination between SOT physicians and haematologists.

AUTHOR CONTRIBUTIONS

N.J., O-E.B. and R.H. conceived, designed the study and wrote the article. DP supervised DSA and cell-free DNA analysis. CP performed ctDNA monitoring. All authors reviewed the manuscript, provided final approval for the article and are accountable for all aspects of the work.

TABLE 1 Management of immunosuppressive treatment during CAR T-cell therapy (references in Supplementary material).

Study	Transplanted organ	Type of CAR T cell	IS at leukapheresis	IS at CAR T-cell infusion	IS after CAR T-cell infusion	Day IS resumed after CAR T cell	Transplant rejection after CAR T-cell infusion	Response to CAR-T	IS at time of assessment
Current report	Kidney	Axi-cel	Corticosteroids	None	Tacrolimus, corticosteroids	180	No	CR (6 m)	None
Ibrahim 2023[S1]	Liver Liver Kidney Kidney	Axi-cel Axi-cel Axi-cel Axi-cel	None None Tacrolimus, corticosteroids[a] Corticosteroids	None None Corticosteroids[a] Corticosteroids[a]	Tacrolimus Tacrolimus Corticosteroids Corticosteroids	120 36 - -	Yes (15 m) No No No	CR (36 m) PD (2 m) CR (36 m) PD (3 m)	Tacrolimus Tacrolimus Corticosteroids Corticosteroids
Portuguese 2023[S2]	Kidney	Liso-cel	Corticosteroids[a]	Corticosteroids[a]	Tacrolimus, corticosteroids	65	No	CR (11 m)[c]	Tacrolimus
Veit 2023[S3]	Lung	Axi-cel	Tacrolimus	Corticosteroids[a]	Tacrolimus, corticosteroids	25	No	CR (1 m)	None
McKenna 2023[S4]	14 Kidney 3 Liver 2 Heart 1 intestine 1Kidney/pancreas 1 Lung	17 Axi-cel 4 Tisa-cel 1 Brexu-cel	16 None 4 corticosteroids[a] 1 tacrolimus, corticosteroids[a] 1 tacrolimus	14 None 6 corticosteroids[a] 1 tacrolimus, corticosteroids[a] 1 tacrolimus	10 corticosteroids 5 tacrolimus 3 None 2 tacrolimus, corticosteroids 1 sirolimus 1 everolimus	Mean: 107 (10–450)	3/22 (3 kidney at 1,4,15 m)	12 CR 2 PR 4 SD 4PD (5-112 m)	ND
Oren 2022[S5]	Heart + Kidney	Liso-cel	Tacrolimus, corticosteroids[a]	Tacrolimus, corticosteroids[a]	Tacrolimus, corticosteroids	-	No	CR (6 m)	Tacrolimus, corticosteroids
Rosler 2022[S6]	Kidney	Tisa-cel	None	None	None	-	No	CR (26 m)	None
Zhu 2022[S7]	HSCT	CD22-CAR T cell (NS)	None	None	None	-	No	PD (1 m)	MMF
de Nattes 2022[S8]	Kidney	Tisa-cel	None	None	Corticosteroids	10	No	PD (3 m)	None
Hernani 2021[S9]	Kidney	Axi-cel	Corticosteroids[a]	Corticosteroids[a]	Corticosteroids	-	No	CR (10 m)	None
Feng 2021[S10]	Kidney	CD19 CAR T cell (NS)	Tacrolimus	Tacrolimus	Tacrolimus	-	No	PR (4.5 m)	Tacrolimus
Dang 2021[S11]	Heart	Axi-cel	Tacrolimus, corticosteroids[a]	Tacrolimus, Corticosteroids[a]	Tacrolimus, corticosteroids	-	No	CR (6 m)	Tacrolimus, corticosteroids
Yan 2021[S12]	HSCT HSCT	CD19 + CD22 donor CAR-T CD19 + CD22 donor CAR-T	None Ciclosporine, MMF	None Ciclosporine, MMF	None Ciclosporine, MMF	- -	No No	CR (10 m) CR (6 m)	None Ciclosporine, MMF
Mamlouk 2021[S13]	Kidney Kidney Kidney	Axi-cel Axi-cel Axi-cel	Corticosteroids[a] None Corticosteroids[a]	Corticosteroids[a] None Corticosteroids[a]	Corticosteroids Corticosteroids Corticosteroids	- 60 -	borderline No No	CR (28 m) CR (3 m) PD (3 m)	Corticosteroids None Corticosteroids
Luttwak 2021[S14]	Kidney Kidney Liver	Tisa-cel Tisa-cel Tisa-cel	Tacrolimus Tacrolimus Tacrolimus	Tacrolimus Tacrolimus Tacrolimus	Tacrolimus Tacrolimus Tacrolimus	- - -	No No No	CR (3 m) CR (9 m) PR (3 m)	Tacrolimus Tacrolimus Tacrolimus
Melilli 2021[S15]	Kidney	Tisa-cel	Corticosteroids[a]	Corticosteroids[a]	Corticosteroids[b]	-	No	CR (36 m)	Corticosteroids
Krishnamoorthy 2021[S16]	Heart Kidney + pancreas Kidney	Axi-cel Axi-cel Axi-cel	Tacrolimus, corticosteroids[a] Tacrolimus, corticosteroids[a] None	Tacrolimus, corticosteroids[a] Sirolimus None	Tacrolimus, corticosteroids Sirolimus None	-	No No No	SD (3 m) PD (1 m) PD (1 m)	None ND ND

(Continues)

TABLE 1 (Continued)

Study	Transplanted organ	Type of CAR T cell	IS at leukapheresis	IS at CAR T-cell infusion	IS after CAR T-cell infusion	Day IS resumed after CAR T cell	Transplant rejection after CAR T-cell infusion	Response to CAR-T	IS at time of assessment
Wang 2021[S17]	Liver	CD19 CAR-T (NS)	None	None	None	-	No	CR (16m)	None
All studies 49 patients	33 kidney (2 PAK) 7 liver 5 heart (1 + kidney) 3 HSCT 2 lung 1 intestine	31 Axi-cel 10 Tisa-cel 2 Liso-cel 1 Brexu-cel 5 NS	25 None 11 corticosteroids[a] 6 tacrolimus 6 tacrolimus, corticosteroids[a] 1 ciclosporine, MMF	24 None 14 corticosteroids alone[a] 5 tacrolimus 4 tacrolimus, corticosteroids[a] 1 sirolimus 1 ciclosporine, MMF	8 None 18 corticosteroids[a] 11 tacrolimus 8 tacrolimus, corticosteroids[a] 2 sirolimus 1 everolimus 1 ciclosporine, MMF		5/49 (4 kidney + 1 liver)	29 CR 4 PR[d] 5 SD 11 PD	9 None 7 tacrolimus 5 corticosteroids 2 tacrolimus, corticosteroids 1 ciclosporine, MMF[e]

Abbreviations: Axi-cel, axicabtagene ciloleucel; Brexu-cel, brexucabtagene autocel; CNS, central nervous system; CR, complete remission; HSCT, haematopoietic stem cell transplantation; Liso-cel, lisocabtagene maraleucel MMF, mycophénolate mofétil; ND, no data reported; NS, not specified; PAK, pancreas and kidney transplantation; PD, progressive disease; RTH, radiotherapy; SD, stable disease; Tisa-cel, tisagenlecleucel.

[a]Low-dose corticosteroids.

[b]Dose increased because of acute kidney injury.

[c]Second CR after relapse managed by RIC and radiation.

[d]PD before receiving CAR-T infusion.

[e]No data available for the other patients.

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CONFLICT OF INTEREST STATEMENT

RH received honoraria from Bristol-Myers Squibb, MSD, Gilead, Kite, Roche, Novartis, Janssen, Celgene and ADC therapeutics. CP received honoraria from AstraZeneca. The remaining authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

Most data from the patient and literature analysis are provided in the manuscript, but more can be provided upon reasonable request by the corresponding author.

ETHICS STATEMENT

This report describes the clinical course of a patient managed in a hospital context and did not require approval.

PATIENT CONSENT

The patient provided consent at hospitalization.

MATERIAL FROM OTHER SOURCES

None.

CLINICAL TRIAL REGISTRATION

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.