Received: 27 January 2021 | Revised: 30 March 2021 | Accepted: 23 April 2021

DOI: 10.1111/ajt.16628

CASE REPORT

Successful treatment of Epstein–Barr virus–associated primary central nervous system lymphoma due to post-transplantation lymphoproliferative disorder, with ibrutinib and third-party Epstein–Barr virus–specific T cells

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Funding information
Mater Foundation

Primary central nervous system lymphoma (PCNSL) occurring following organ transplantation (post-transplantation lymphoproliferative disorder [PTLD]) is a highly aggressive non-Hodgkin lymphoma. It is typically treated with high-dose methotrexate-based regimens. Outcomes are dismal and clinical trials are lacking. It is almost always Epstein–Barr virus (EBV) associated. Two patients (CA1-2) presented with EBV-associated PCNSL after renal transplant. CA1 was on hemodialysis and had prior disseminated cryptococcus and pseudomonas bronchiectasis, precluding treatment with methotrexate. CA2 was refractory to methotrexate. Both were treated off-label with the first-generation Bruton's tyrosine kinase inhibitor ibrutinib for 12 months. Cerebrospinal fluid penetration at therapeutic levels was confirmed in CA1 despite hemodialysis. Both patients entered remission by 2 months. Sequencing confirmed absence of genetic aberrations in human leukocyte antigen (HLA) class I/II and antigen-presentation/processing genes, indicating retention of the ability to present EBV-antigens. Between Weeks 10 and 13, they received third-party EBV-specific T cells for consolidation with no adverse effects. They remain in remission ≥34 months since therapy began. The strength of these findings led to an ongoing phase I study (ACTRN12618001541291).

KEYWORDS
cancer / malignancy / neoplasia: hematogenous / leukemia / lymphoma, complication: malignant, dialysis: hemodialysis, hematology / oncology, immunobiology, infection and infectious agents - viral: Epstein-Barr Virus (EBV), translational research / science

Abbreviations: BBB, blood–brain barrier; BCR, B cell receptor; BTK, Bruton's tyrosine kinase; Ch1, channel 1; CR, complete remission; CSF, cerebrospinal fluid; DLBCL, diffuse large B cell lymphoma; EBER, EBV-encoded small RNAs; EBV, Epstein–Barr virus; G-CSF, granulocyte colony stimulating factor; HLA, human leukocyte antigen; IL, interleukin; Indel, insertion–deletion; ITK, interleukin-2 inducible kinase; LMP1, latent membrane protein-1; MTX, methotrexate; NTC, no template control; PBMC, peripheral blood mononuclear cells; PCNSL, primary central nervous system lymphoma; PRM, parallel reaction monitoring; PTLD, post-transplantation lymphoproliferative disorder; qPCR, quantitative polymerase chain reaction; TME, tumor microenvironment.

1 | INTRODUCTION

Post-transplantation lymphoproliferative disorder (PTLD) comprises a variety of histopathologic entities that arise due to impaired T cell immune surveillance due to iatrogenic immunosuppression after organ transplantation. Approximately half of cases are EBV-associated.[1] Unlike systemic PTLD, primary central nervous system lymphoma (PCNSL) due to PTLD usually occurs many years after transplantation[2] and is almost always EBV associated (with a viral latency III pattern).[3] It is confined to the brain, eyes, and cerebrospinal fluid (CSF) without evidence of systemic spread. The most frequently observed subtype is monomorphic PTLD with diffuse large B cell lymphoma (DLBCL) histology.[4]

Outcomes for EBV-associated PCNSL due to PTLD are dismal, with median progression free survival just 8 months.[2] The optimal management is unknown, and there are no consensus guidelines. We outline two cases of EBV-associated PCNSL following renal transplantation. They were treated with a novel combination therapy of ibrutinib and third-party EBV-specific T cells and successfully entered sustained remission.

2 | METHODS

2.1 | Patients

Patients CA1 and CA2 had monomorphic PTLD (DLBCL subtype) histologically confirmed on formalin-fixed paraffin-embedded tissue. EBV-encoded small RNAs (EBER) in situ hybridization was performed to detect EBV within malignant B cells as previously described.[5] They were treated under the Australian Therapeutic Goods Administration compassionate access scheme (Table 1). Additional assays were performed with informed consent as part of a study approved by the relevant institutional regulatory board in concordance with the Declaration of Helsinki.[4] Treatment response evaluation followed the International Primary CNS Lymphoma Collaborative Group guidelines.[6] Quantitative EBV-DNA polymerase chain reaction (qPCR) used previously published methodology.[7]

2.2 | Sequencing and gene expression

A capture-hybrid targeted sequencing panel was used to identify mutations and copy number aberrations in antigen presentation/processing (*CIITA*, *NLRC5*, *TAP1*, *TAP2*, *β2 M*, *CD58*, *CTSS*, and HLA class I and II) as well as genes that are known to be frequently mutated in EBV-negative PCNSL (including *MYD88*^{L265P}, *CD79B*, and *PIM1*) as published.[4] Gene expression was digitally quantified for Lymph2Cx cell-of-origin and EBV-genes using the nCounter platform (NanoString) as previously outlined,[8] with viral latency assigned as previously reported.[9]

TABLE 1 Clinical characteristics and outcomes of the two EBV-associated PCNSL PTLD patients

Patient code	Clinical characteristics	Presentation	Disease characteristics	Adverse effects	Ibrutinib treatment duration	Outcome	Genetic characteristics
CA1	42 years M; 7-year post-renal-pancreas transplant (PTLD), thrice weekly hemodialysis dependent; prior disseminated cryptococcus and pseudomonas bronchiectasis; no prior therapy (unfit for high-dose MTX)	Seizures; ECOG 1; plasma EBV-DNA not detectable	Right frontal lobe lesion, with DLBCL histology	Ibrutinib: Grade 3 anemia and Grade 2 rash requiring temporary dose reductions, and Grade 3 flare of bronchiectasis requiring brief cessation/no third-party EBV-specific T cell adverse effects	12 months	CR by 2 months and ongoing 14 months from end of therapy	No mutations; HLA-class I/II intact
CA2	30 years F; 1-year post-renal transplant (PTLD); refractory to high-dose MTX and rituximab	Seizures and visual field defect; ECOG 1; plasma EBV-DNA not detectable	Multiple enhancing brain lesions (largest right parietal), with DLBCL histology	Ibrutinib: Grade 2 skin rash, nail changes, interstitial pneumonitis requiring temporary dose reduction/no third-party EBV-specific T cell adverse effects	12 months	CR by 2 months and ongoing 13 months from end of therapy	*SETDB1* missense mutation; HLA-class I/II intact

Abbreviations: CR, complete remission; DLBCL, diffuse large B cell lymphoma; EBV, Epstein–Barr virus; ECOG, Eastern Cooperative Oncology Group performance status; F, female; HLA, human leukocyte antigen; M, male; MTX, methotrexate; PTLD, post- transplantation lymphoproliferative disorder.

TABLE 2 Details of third-party EBV-specific T cells

	CA1			CA2		
		Recipient	T cell donor		Recipient	T cell donor
HLA match	HLA-A	02:01 / 02:01	02:01 / 24:02	HLA-A	24/26	02:01/24:02
	HLA-B	08:01 / 40:01	08:01 / 44:02	HLA-B	38/15:07	08:01/44:02
	HLA-C	03:04 / 07:01	05:01 / 07:01	HLA-C	03:03/12:03	05:01/07:01
	HLA-DRB1	04:01 / 13:02	03:01 / 04:01	HLA-DRB1	1/13	03:01/04:01
	HLA-DQB1	03:02 / 06:04	02:01 / 03:01	HLA-DQB1	05/06	02:01/03:01
EBV epitope mapping[a]	EBV consensus	84.9% CD107+, 67.2% IFNγ+, 54.3% TNFα+ of CD3+ 87.7% CD107+, 67.4% IFNγ+, 55.7% TNFα+ of CD8+ 3.3% CD107+, 1.7% IFNγ+, 2.2% TNFα+ of CD4+		EBV consensus	84.9% CD107+, 67.2% IFNγ+, 54.3% TNFα+ of CD3 87.7% CD107+, 67.4% IFNγ+, 55.7% TNFα+ of CD8+ 3.3% CD107+, 1.7% IFNγ+, 2.2% TNFα+ of CD4+	

Note: EBV-specific T cell activity was presented through HLA-A*02:01 and HLA-B*08:01 for patient CA1 and HLA-A*24:02 for patient CA2.
[a]Intracellular cytokine and degranulation by flow cytometry.

2.3 | Third-party EBV-specific T cell generation

Third-party EBV-specific T cells were manufactured by Cellular Therapies, NSW Government Health Pathology, using activation marker selection of T cells exposed to viral peptides. Details are provided in the Supplementary. The proportion of third-party EBV-specific T cells in each product is shown in Table 2.

2.4 | Ibrutinib pharmacokinetic assays

A stock of ibrutinib-D5 (Cayman Chemical) was prepared at 0.5 mg/ml with methanol. Working solutions were prepared in 40% acetonitrile. Ibrutinib-D5 was used as an internal standard at a concentration of 50 ng/ml. Protein in CSF samples was removed by precipitation with 4 volumes of acetonitrile at room temperature. Precipitates were removed by centrifugation at 13 000 *g* for 10 min. The supernatant (containing the metabolite) was diluted 1:2 before LC-MS/MS analysis. Five-microliter processed samples was separated with easy nano-liquid chromatography (nLc) 50 cm easy spray column (Thermo Fisher). The easy nLc gradient was 0 min, 3%; 1 min, 72%; 8 min, 85%; 8.5 min, 95%; 16 min, 95%; 19 min, 3%. The metabolites were analyzed on a Q-Exactive plus with parallel reaction monitoring targeting against ibrutinib (C25H24N6O2, 441.2034 m/z) and deuterium labeled ibrutinib (ibrutinib-D5: C25H19H'5N6O2, 446.2347 m/z). The metabolites were eluted at 13.72 min. Mass spectrometry data were analyzed with Skyline for ibrutinib (441.2034 > 138.0900) and ibrutinib-D5 (446.237 > 138.0900).

2.5 | Ultrasensitive droplet digital PCR

Assessment of the persistence of infused third-party EBV-specific T cells was performed for patient CA2 using previously published methods.[10] Informative insertion and deletion polymorphisms (indels) between donor and recipient were assessed using a commercial qPCR kit (KMRtype, GenDx). An assay for an indel present only in the donor was selected for the droplet digital PCR microchimerism assay using the indel probe (GenDx) and a reference gene (RPP30; Bio-Rad); 1200 ng of genomic DNA derived from peripheral blood mononuclear cells (PBMC) collected at various time points during treatment was assessed and quantified against the reference gene to determine the percentage of circulating donor EBV-specific T cells. Time points with less than three positive droplets were considered negative.

3 | RESULTS

3.1 | A rationally designed induction/consolidation strategy given off-label in two patients

CA1 was a prior renal/pancreatic organ recipient, and CA2 had had a renal transplant. Consistent with emerging data that EBV induces an atypical germinal center reaction,[4,11] NanoString gene expression showed germinal center B cell Lymph2Cx cell of origin with a EBV-latency type III. There were no mutations in B cell receptor (BCR) pathway or the cell/cycle adhesion molecule PIM1 or the ibrutinib resistance gene *CARD11*; and no copy number loss in HLA-class I/II or gene aberrations in antigen presentation molecules observed. Further characteristics are provided in Table 1. Both patients were initially treated with reduction of immunosuppression (involving cessation of mycophenolate, reduction of calcineurin drugs and continuation of steroids) upon PTLD presentation without improvement. CA1 was on thrice weekly (Monday/Wednesday/Friday) hemodialysis for a nonfunctioning transplanted kidney. Methotrexate is renally excreted. CA1 also had a history of prior disseminated cryptococcus and pseudomonas bronchiectasis. These reasons combined precluded high-dose methotrexate therapy. CA2 was refractory to conventional first-line high-dose methotrexate and rituximab-based therapy.

Both patients commenced oral ibrutinib at 560 mg once daily (CA1 had a 1-week lead in at 420 mg) along with trimethoprim/sulfamethoxazole and valaciclovir prophylaxis. Rituximab (375 mg/m^2) was also given at Weeks 1–4 and at 20, 30, 40, and 50 weeks to CA1. In addition to potential anti-PCNSL activity, it was felt that rituximab might reduce the risk in CA1 of pancreatic allograft rejection. CA1 was receiving oral posaconazole at 300 mg once daily at presentation (for prior cryptococcus). Although ibrutinib is metabolized via cytochrome P450 3A4 (CYP3A4) and posaconazole is a known CYP3A4 inhibitor, CA1 was able to receive ibrutinib for 12 months, except for temporary dose reductions to correct for grade three anemia and grade two rash, and a 1-week cessation to correct for a grade three flare of bronchiectasis. Details of patient characteristics and adverse effects and outcomes are provided in Table 1.

CA1/2 both entered complete remission (CR) at the time of the first re-staging scan at 2 months and remain in remission 36 (CA1) and 34 (CA2) months since treatment cessation (Figure 1A). MRI brain scan images of CA1 taken at presentation and 16 months post therapy are shown in Figure 1B. They received consolidation with ×4 infusions of partially HLA-matched third-party EBV-specific T cells, each given a week apart, at Weeks 10, 11, 12, and 13 at $2 \times 10^7/m^2$ per infusion. As treatment was not part of a controlled study, there were limited biological specimens available for correlative studies. With CA1, only pharmacokinetic assays, and for CA2, only microchimerism studies were available.

As CA1 was on hemodialysis and concomitant posaconazole, samples for pharmacokinetic analysis of ibrutinib on paired blood/CSF at Weeks 10 and 17 were collected at 6 h after the ibrutinib dose. At Week 10, samples were taken 1 h after dialysis cessation, whereas the samples at Week 17 were taken on a dialysis-free day. Ibrutinib concentration measured in CSF at Week 17 was similar to those previously reported in patients with PCNSL treated at this dose.[12] Although CSF concentrations were ~11-fold less on hemodialysis days compared to non-dialysis days, a much higher fraction of free drug penetrated and remained in the CSF despite hemodialysis removing most of the drug from the circulation (Figure 1C). In CA2, microchimerism analysis of informative indels showed third-party EBV-specific T cells were detectable at 2 h after the fourth infusion but did not persist long-term within the circulation (Figure 1D).

4 | DISCUSSION

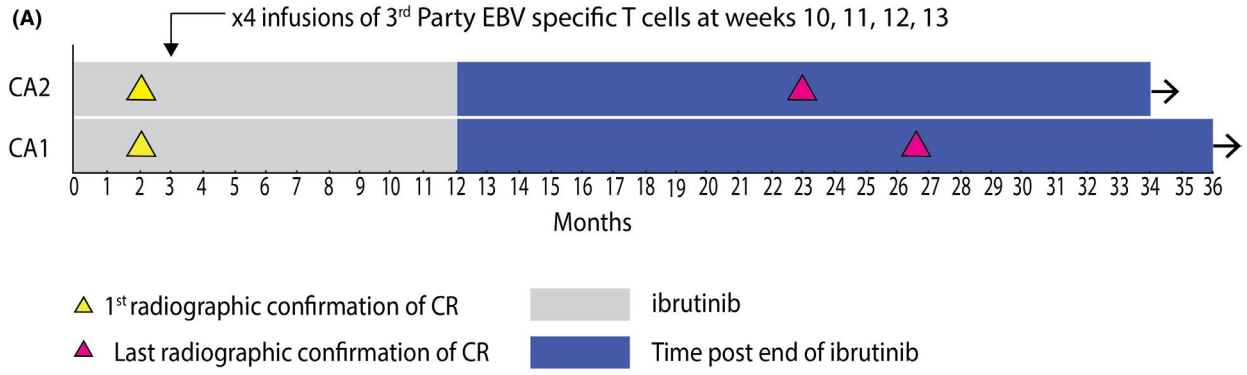
Here, we describe the successful treatment of two challenging patients with EBV-associated PCNSL occurring in the context of PTLD, with a novel targeted combination therapy. Patients were treated on compassionate access with an ibrutinib induction/maintenance regimen for one year. Consolidation was given with third-party EBV-specific T cells. One of the patients was on hemodialysis. They remain in remission ≥34 months since therapy began.

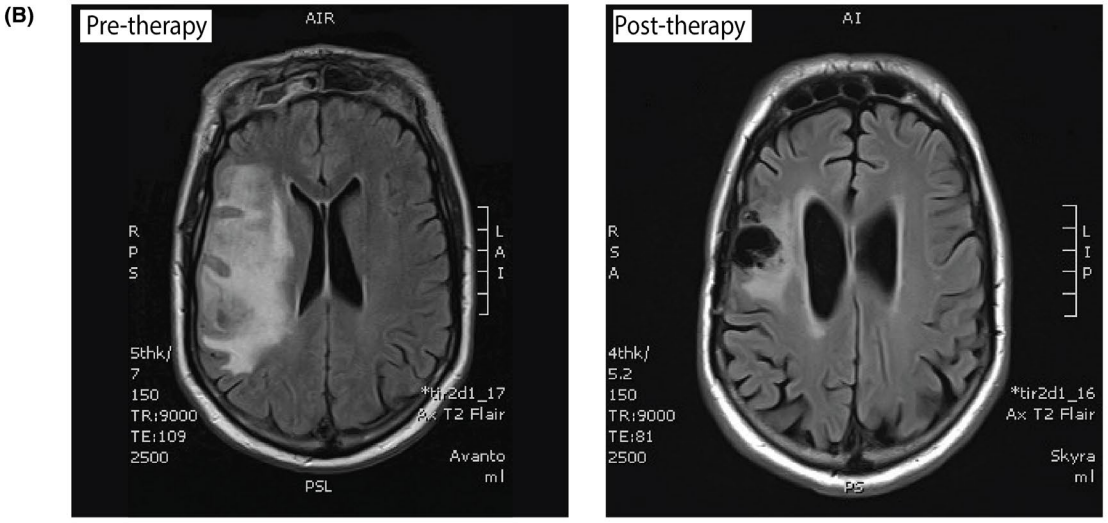
There were multiple reasons why ibrutinib might be theoretically beneficial to EBV-associated PCNSL in the context of PTLD. It is a small molecule that crosses the blood–brain barrier (BBB) with established efficacy in EBV-negative PCNSL.[12,13] Furthermore, EBV-positive leukemic T cell lines as well as in vivo transformed B cells cultured in the presence of ibrutinib have decreased survival.[14] It potently and irreversibly inhibits Bruton's tyrosine kinase (BTK) and interleukin-2 inducible kinase (ITK). However, mutations in the BCR signaling molecule CARD11 and cell cycle/adhesion gene PIM1 are associated with complete or partial ibrutinib resistance in PCNSL and/or systemic DLBCL.[12,15] Notably, these mutations were absent in CA1 and CA2. Furthermore, EBV-associated PCNSL was recently shown to have a tolerogenic tumor microenvironment (TME) with transcriptome analysis showing elevated *CD68*, *CD163*, *PD-L1*, *PD-L2*, *LAG-3*, and *TIM-3* genes indicative of raised macrophage and immune-checkpoint expression.[4] Importantly, ibrutinib is believed to induce beneficial effects on the TME, which may have augmented EBV-specific T cell immunity. It depletes T-helper-2 cells and is licensed for use to ameliorate chronic graft versus host disease via inhibition of ITK. This suggests that it would be unlikely to mediate renal allograft rejection, making it an attractive therapeutic option in the setting of PTLD.[16,17]

A confounding factor is that patient CA1 also received systemic rituximab. In addition to potential therapeutic benefit, rituximab is known to provide immunosuppression without impacting EBV-specific T cell immunity.[18] Although systemic rituximab conferred no benefit in a recent randomized trial of EBV-negative PCNSL (in the non-immunosuppressed),[19] the possibility that rituximab induced and/or contributed to the sustained remission observed in that patient cannot be excluded.

Although ibrutinib has minimal renal clearance, information on the safety and efficacy of ibrutinib therapy in patients with lymphoma

FIGURE 1 Clinical response and correlative assays. (A) Swimmers plot demonstrating treatment response and duration and timing of ibrutinib/third-party EBV-specific T cells; (B) axial T2 Flair magnetic resonance imaging (MRI) brain scan images, taken at initial presentation (prior to biopsy) and a representative scan (of multiple MRI scans) following initiation of therapy (this one was taken at 16-month post). The "pre-therapy" image shows a lesion in the right frontal lobe, extending posteriorly to involve the deep white matter of the post central gyrus and inferior parietal lobe. The "post-therapy" image shows a cystic cavity and surrounding gliosis (scarring) in the right front lobe at the site of craniotomy and previous lesions, with no residual or new lymphoma identified. (C) CSF and plasma ibrutinib concentrations in ng/ml and *corr. (corrected) ratio, which refers to the CSF/plasma ratios corrected for 97.3% protein binding, 6 h after oral ibrutinib for CA1; (D) persistence of infused third-party EBV-specific T cells for CA2 in peripheral blood was assessed using a droplet digital microchimerism assay. Third-party EBV-specific T cells were administered on Weeks 10, 11, 12, and 13, with blood taken pre- and post-infusion (pre: morning prior to infusion; post: 2-h post-infusion) on Days D1, D7, D14, D21, and D159 after the first infusion. Third-party EBV-specific T cells were only detectable on D21, 2 h postfourth infusion at 0.023% (limit of detection of this assay 0.008%). Third-party EBV-specific T cells were not detected at any other time points with less than 3 positive droplets (i.e., amplitude equivalent to positive control) were considered negative. CR, complete remission; Ch1, channel 1; NTC, no template control


(A)
x4 infusions of 3rd Party EBV specific T cells at weeks 10, 11, 12, 13
CA2
CA1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
Months
1st radiographic confirmation of CR
Last radiographic confirmation of CR
ibrutinib
Time post end of ibrutinib


(B)
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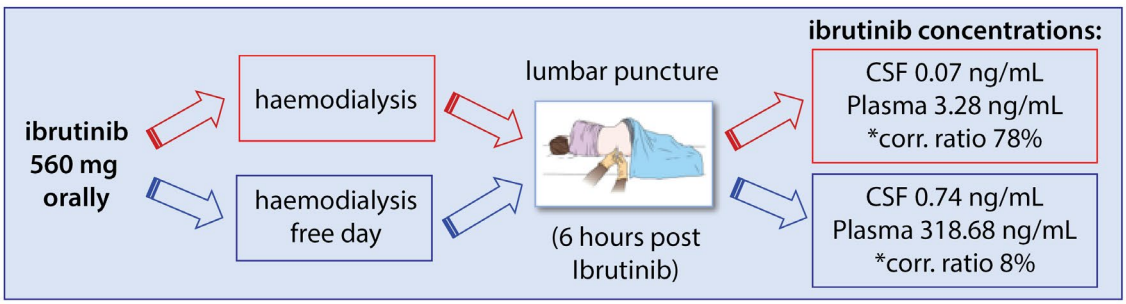
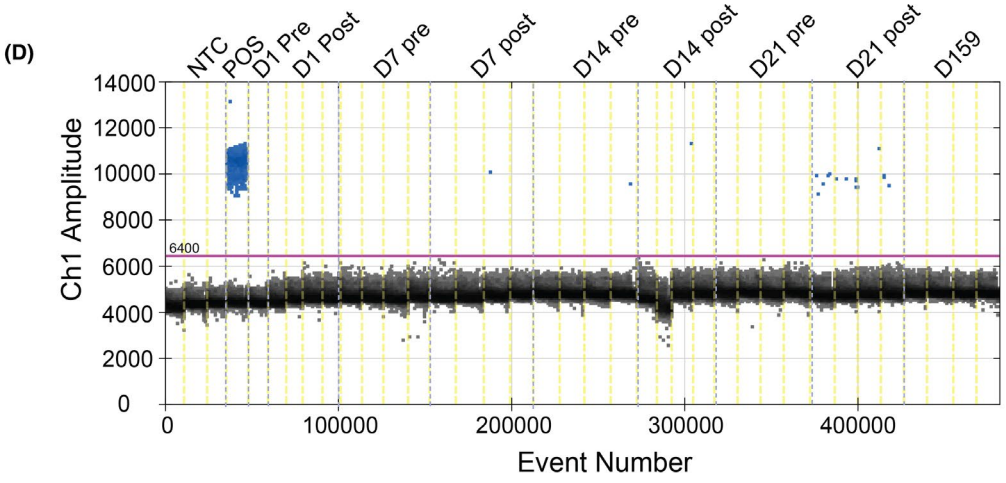

(C)
ibrutinib concentrations:
ibrutinib 560 mg orally
haemodialysis
haemodialysis free day
lumbar puncture
(6 hours post Ibrutinib)
CSF 0.07 ng/mL
Plasma 3.28 ng/mL
*corr. ratio 78%
CSF 0.74 ng/mL
Plasma 318.68 ng/mL
*corr. ratio 8%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requiring hemodialysis is limited to a case report of a patient with systemic mantle cell lymphoma.[20] No pharmacokinetic assays were performed.[20] To our knowledge, successful treatment of a patient with PCNSL using ibrutinib while on hemodialysis has not been previously reported. Ibrutinib concentrations in CSF were markedly lower in CA1 on the hemodialysis day compared to the non-dialysis day, although still detectable. Ibrutinib is a CYP3A4 substrate, and levels were also likely influenced by inhibition of CYP3A4 metabolism by posaconazole. Ibrutinib is known to be associated with a number of serious adverse events in PCNSL at the dose administered.[21] However, although other BTK inhibitors are possibly better tolerated,[22] their ability to cross the BBB remains to be established.

Tumors in both patients expressed the EBV oncogene latent membrane protein-1 (LMP1). In EBV-associated lymphomas, PD-L1 and PD-L2 expression is amplified by LMP1 acting via the JAK/STAT pathway.[23] Although checkpoint blockade shows promise in small patient series with EBV-negative PCNSL and AIDS-related PCNSL, it is contraindicated in PTLD (although some advocate using it with caution) because of the potential for graft rejection. However, the distinct immunobiology of EBV-associated PCNSL does provide therapeutic opportunities in terms of cellular immunotherapy. Restoration of EBV-specific T cell immunity with third-party EBV-specific T cells, chosen on the basis of the best HLA match and in vitro effector function, appears safe and has been shown to induce clinical response in EBV positive lymphomas and to cross the BBB.[24,25] As both CA1-2 were in remission prior to infusion, no comments can be made regarding the efficacy of third-party EBV-specific T cells, only that no adverse effects were detected. The lack of long-term engraftment minimizes the theoretical risks posed by future donor T cell mediated graft rejection.

In summary, based on the cumulative clinical and biological rationale, two patients with EBV-associated PCNSL (both with PTLD) were treated with a novel targeted therapy of ibrutinib induction and third-party EBV-specific T cell consolidation. Neither had mutations associated with ibrutinib resistance nor copy number loss of HLA-class I/II. Both patients achieved sustained CR. Controlled studies involving larger cohorts of patients are required to establish broader applicability. The encouraging clinical experience to date resulted in an ongoing phase one Australasian Leukemia/Lymphoma Group clinical trial of ibrutinib and third-party EBV-specific T cells for EBV-associated B cell lymphomas in the immunosuppressed (ACTRN12618001541291).

ACKNOWLEDGMENT

The support of the Mater Foundation is gratefully acknowledged.

DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. M.K.G. is receiving free ibrutinib drug and distribution (but no direct financial support) from Janssen for an ongoing investigator initiated clinical trial. The other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Law SC, Hoang T, O'Rourke K, et al. Successful treatment of Epstein–Barr virus–associated primary central nervous system lymphoma due to post-transplantation lymphoproliferative disorder, with ibrutinib and third-party Epstein–Barr virus–specific T cells. *Am J Transplant*. 2021;21:3465–3471. https://doi.org/10.1111/ajt.16628