Adoptive Therapy with EBV-Specific T Cells for Treatment of CNS EBV Post-Transplant Lymphoproliferative Disease Arising after Hematopoietic Stem Cell Transplant or Solid Organ Transplant

Susan Prockop, MD[1], Stephanie Suser[1], Ekaterina Doubrovina, MD, PhD[2]*, Hugo R. Castro-Malaspina, MD[3], Esperanza B. Papadopoulos, MD[3], Craig S. Sauter, MD[3], James W. Young, MD[3], Victoria Szenes, PNP[1]*, Alison Slocum, MA[2]*, Karim Baroudy, MS[2]* and Richard J. O'Reilly, MD[1]*

[1]Department of Pediatrics, BMT Service, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY; [3]Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Adoptive immunotherapy with EBV-specific T-cells (EBV-CTLs) derived from primary hematopoietic transplant donors is effective in the treatment of EBV disease complicating allogeneic hematopoietic stem cell transplant (HCT). In addition, third party donor-derived EBV-CTLs (tabelecleucel) have demonstrated efficacy in the treatment of EBV post-transplant lymphoproliferative in the setting of both HCT and solid organ transplant (SOT). While the introduction of first line therapy with rituximab has reduced the mortality associated with EBV-PTLD, EBV PTLD involving the central nervous system (CNS) remains a particularly ominous event as the efficacy of rituximab for CNS disease is limited by poor CNS bioavailability.

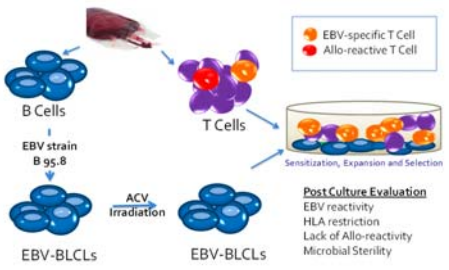
Between 1996 and 2016 we treated nineteen patients for EBV-PTLD involving the CNS arising after HCT (12) or SOT (7). These patients received EBV-CTLs from their primary transplant donor (7), tabelecleucel from a third-party donor (11) or from both types of donor (1). Patients were treated for either isolated CNS disease (10) or CNS and systemic disease (9). Patients developing EBV-PTLD after HCT were recipients of T Cell Depleted (N=6), cord blood (N=3) and conventional (N=3) transplant. Those developing EBV-PTLD after SOT had undergone renal (N=4) heart (1) liver (1) and heart/liver (1) transplants. All of these patients had received prior therapy including rituximab (N=17), radiation therapy (N=6), and chemotherapy (N=9).

Primary donor EBV-CTLs were generated from EBV seropositive hematopoietic transplant donors at the time of or after the patient underwent transplant. Third party tabelecleucel were selected from a bank of 330 lines generated under GMP conditions from normal HCT donors who specifically consented to use of their T cells in patients other than their designated transplant recipient. Selection of third party tabelecleucel lines was made on the basis of HLA restriction by at least one HLA allele shared by the patient's tumor and the HCT donor, and matching for ≥ 2/10 recipient alleles. Patients received 3 weekly infusions of approximately 1-2x10^6 T cells/kg/infusion. Patients were sequentially evaluated for clinical and radiographic response, and quantifications of EBV DNA by PCR. Patients not achieving a complete response to an initial cycle of EBV directed cellular therapy were eligible to receive subsequent cycles of cells from either the same or a different donor. Responses were assessed 21-35 days after the first of each cycle of EBV-CTLs. Responses were evaluated based on Lugano criteria with CNS disease being assessed by MRI, CSF or thalium scan. Two patients treated for CNS and systemic disease had simultaneous therapy of their CNS disease and achieved responses of both CNS and systemic disease but the CNS specific response could not be attributed to cell therapy alone.

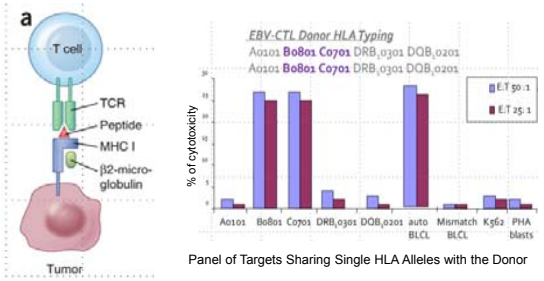
Of the 19 patients, 7 achieved complete responses and 5 durable partial responses for an overall response rate of 63%. The one-year overall survival (OS) for this cohort of 19 patients was 60% with responding patients experiencing one year OS of 91.7% and non-responding patients one year OS of just 14.3%. Eight of the 10 patients treated for isolated CNS disease responded to adoptive EBV directed T cell therapy. One-year overall survival for patients treated for isolated CNS disease is 70% and with CNS and systemic disease is 55.6%. Toxicities associated with infusions in this cohort are limited with 8 patients experiencing adverse events of ≥ grade 3 severity with one patient experiencing a possibly related grade 3 event

This study demonstrates a high response rate among patients with otherwise refractory EBV PTLD affecting the CNS. Adoptive therapy with EBV directed cellular therapy (primary donor or third party derived) can effectively treat this otherwise frequently lethal complication. The availability of 3rd party tabelecleucel enables treatment early in the course of disease and may thereby improve response rates while minimizing toxicity from chemotherapy.

ex vivo Generation of EBV-specific CTL



EBV-Specific CTLs are Characterized by HLA Restriction



Panel of Targets Sharing Single HLA Alleles with the Donor

From Hinrich CS and Restivo NP. 2013. *Nature Biotechnol* 31; 999-1008

Bank of EBV-specific CTLs

Inventory

A. 330 HSCT donor-derived EBV-specific T Cell lines

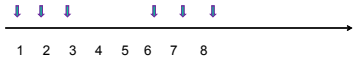
Characterization

A. Consented for third party use
B. Defined HLA type at high resolution
C. Defined EBV specificity and HLA restriction
D. Demonstrated lack of allo-reactivity or non-specific cytotoxicity
E. Microbiologically sterile, and containing<5EU of endotoxin/ml dose
F. Rapidly available for "off-the-shelf" use - able to find a line for >98% of patients

Treatment

Third Party EBV-CTL lines from primary donor or selected based on matching for at least 2/8 HLA alleles (A, B, C and DR) at high resolution restriction by an HLA allele shared by the target

1 dose/week x 3 1- 2 x 10^6 T cells/kg/dose infused IV over 5 minutes



•Safety and Clinical Endpoints

1) Infusion related toxicity, alterations of organ function, α-HLA antibodies
2) Systemic response by clinical and radiographic criteria
3) CNS disease was assessed by MRI, CSF, or thallium scan
4) EBV by PCR (if measurable)
5) Alterations in circulating CTL precursors by limiting dilution assay

Patients w/o CR or toxicity eligible to receive additional cycles

EBV-CTL Safety Profile

•Adverse events were graded using NCI CTCAE
  •95-024 (NCT00002663) CTCAE 2.0
  •11-130 (NCT01498484) CTCAE 4.0

Cohort	SAEs	Patients	Related	Grade	Description
95-024	9	5	1 possibly	3	Neurologic (seizure)
11-130	7	3	0 possibly	N/A	N/A

- ***•Infusion-Related Toxicities:*** None
- ***•GvHD:*** No de novo GvHD
- ***•Solid Organ Rejection:*** No new episodes
- ***•Cytokine Release Syndrome:*** None observed

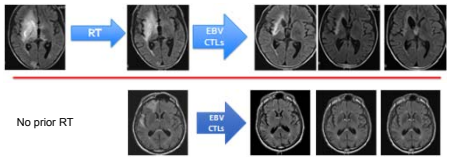
Patients with EBV Disease Involving the CNS

Subject No.	Group	Transplant type	Disease Outside CNS	Prior Ritux	Prior RT	Prior Chemo Systemic/IT	Cell Type	Response to Cells (Systemic)	Response to Cells (CNS)
1	HCT	TCD BMT	No	No	Yes	No/No	Primary	N/A	Complete Remission
2	HCT	TCD BMT	No	Yes	No	No/No	Primary	N/A	Stable Disease
3	HCT	TCD BMT	Yes	Yes	No	HU/No	Primary	Complete Remission	Complete Remission
4	HCT	TCD PBSCT	Yes	Yes	No	Yes/No	Primary	Progression of Disease	Progression of Disease
5	HCT	TCD PBSCT	No	Yes	No	No/No	Primary	N/A	Progression of Disease
6	HCT	TCD PBSCT	Yes	Yes	No	No/No	Primary	Progression of Disease	Progression of Disease
7	HCT	cBMT	Yes	Yes	No	No/No	Third Party	Partial Remission	Not Evaluable
8	HCT	cBMT	Yes	Yes	No	No/No	Third Party	Complete Remission	Not Evaluable
9	HCT	CBT	No	Yes	No	No/Yes	Third Party	N/A	Complete Remission
10	HCT	CBT	Yes	Yes	Yes	HU/No	Third Party	Complete Remission	Complete Remission
11	HCT	PBSCT	Yes	Yes	No	Yes/No	Both	Progression of Disease	Progression of Disease
12	HCT	CBT/HAPLO	No	Yes	Yes	Yes/Yes	Third Party	N/A	Partial Remission
13	SOT	Heart/Liver	No	Yes	Yes	Yes/No	Third Party	N/A	Partial Remission
14	SOT	Renal	No	Yes	No	Yes/No	Third Party	N/A	Complete Remission
15	SOT	Liver	No	Yes	Yes	Yes/No	Third Party	N/A	Partial Remission
16	SOT	Renal	No	Yes	No	No/No	Third Party	N/A	Partial Remission
17	SOT	Heart	Yes	Yes	No	Yes/No	Third Party	Progression of Disease	Progression of Disease
18	SOT	Renal	No	Yes	No	No/No	Third Party	N/A	Complete Remission
19	SOT	Renal	Yes	No	Yes	Yes/No	Primary	Progression of Disease	Progression of Disease

3rd Party EBV CTL Therapy in CNS Disease

	N	CNS RT	Residual Disease After CNS RT	CNS PR/CR (%)	NE
Tabelecleucel	11	7*	5	4/4 (73%)	2*
1* Donor	7	2	2	0/2 (29%)	0
Both	1	1	1	0 (0%)	0
Total	19	10	8	4/6 (53%)	2

•Four patients had concomitant CNS RT
  •Two(*) had systemic response but were NE for CNS response
•None of the responding patients (PR/CR) recurred or died of EBV
•One Year OS: 60%
  •1 year OS for responder: 91.7%
  •1 year OS for non-responders: 14.3%
•80% of those treated for isolated CNS disease responded



Conclusions

1. In this cohort the overall response rate was 63% and was even higher in those treated with tabeleuclecel - perhaps reflecting the ready availability of this product.
2. The responses seen with this therapy have been durable and translate into overall survival.
3. The 1-yr (OS) for this cohort of 19 patients was 60%; responders and non-responders experienced 91.7% and 14.3% 1yr OS respectively
4. The safety profile in this patient population appears consistent with our previous observations, with 8 out of 19 patients experiencing serious adverse events of ≥ grade 3 in severity and one patient experiencing a possibly related grade 3 serious adverse event. No specific safety trends were observed.
5. Tabeleuclecel is an appropriate therapy for patients with EBV disease involving the CNS.

Disclosures:

Atara Biotherapeutics has an exclusive license to develop and commercialize this cell therapy program.

Prockop: *Mesoblast:* Research Funding; *Atara Biotherapeutics:* Research Funding. **Doubrovina:** *Atara Biotherapeutics:* Consultancy, Patents & Royalties, Research Funding. **Sauter:** *Juno Therapeutics:* Consultancy, Research Funding; *Sanofi-Genzyme:* Consultancy, Research Funding; *Spectrum Pharmaceuticals:* Consultancy; *Novartis:* Consultancy; *Precision Biosciences:* Consultancy; *Kite:* Consultancy. **O'Reilly:** *Atara Biotherapeutics:*Consultancy, Patents & Royalties, Research Funding.