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 Procopk, MD1, Stephanie Suser4, Ekaterina Dourovina, MD, PhD2, Hugo R. Castro-Malaspina, MD1, Esperanza B. Papadopoulos, MD4, Craig S. Sauter, MD1, James W. Young, MD1, Victoria Szenes, PNP1, Alison Slocum, MA1, Karim Baroudy, MS1, and Richard J. O'Reilly, MD1

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

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 (tableteucleel) have demonstrated efficacy in the treatment of EBV post-transplant lymphoproliferative disorder (PTLD) 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 1998 and 2016 we treated nineteen patients for EBV-PTLD involving the CNS after HCT (12) or SOT (7). These patients received EBV-CTLs from their primary donor (7), tableteucleel from a third party donor (11) or from both types of donor (1). Patients were treated for either isolated CNS disease (16) or CNS and systemic disease (3). Patients developing EBV-PTLD after HCT were recipients of T cell depleted (HDT), cord blood (N=2) and conventional (N=3) transplant. Those developing EBV-PTLD after SOT had undergone renal (N=1) and heart (N=1) transplants. All of these patients had received prior therapy including rituximab (N=17), radiation therapy (N=4), and chemotherapy (N=9).

Primary donor EBV-CTLs were generated from EBV-seropositive hematopoietic transplant donors at the time of the patient undergoing transplant. Third party tableteucleel were selected from a bank of 353 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 tableteucleel lines was based on the lack of HLA restriction by at least one HLA allele shared by the patient’s tumor and the HCT donor and matching for ≥ 210 recipient alleles. Patients received 3 weekly infusions of approximately 1-2 x 10^6 T cells/kg/cohort. 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 courses of cells from either the same or a different donor. Responses were assessed 21-35 days after the first cycle of EBV-CTLs. Responses were evaluated based on Lugano criteria with CNS disease being assessed by MRI, CSF, or thallium scan. Two patients treated for CNS and systemic disease had simultaneous therapy of their CNS and systemic disease. EBV-CTLs and EBV-specific T cells were found to be limited by poor CNS bioavailability.

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 68% 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 cellular therapy. One year overall survival for patients treated for isolated CNS disease was 71% and with CNS and systemic disease was 55.9%. Toxicities associated with infusions included lack of specificity for non-specific cytotoxicity, neurologic toxicity, and transient elevations in liver enzymes.

Tableteucleel is an appropriate therapy for patients with EBV disease involving the CNS. The availability of 3rd party tableteucleel enables treatment early in the course of disease and may thereby improve response rates while minimizing toxicity from chemotherapy.

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