CAR T-cell Therapy for Secondary CNS DLBCL.

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Abstract:
Management of secondary central nervous system involvement (SCNSL) in relapsed or refractory aggressive B-cell lymphomas remains an area of unmet medical need. We report a single center retrospective analysis of seven adult patients with SCNSL who underwent CAR-T therapy for their refractory disease and describe safety of whole brain radiation as a bridging therapy. Six patients (85.7%) achieved a complete response at D+28, while 1 patient had progressive disease. The median progression free survival was 83 days (28 - 219) and a median overall survival was 129 days (32 - 219). Three patients died due to disease progression. Of the 5 patients who received WBRT as bridging therapy, 3 had no ICANS, while 2 had grade 1 and 3, respectively. No grade 4 ICANS was reported in this subset of patients. We conclude that SCNSL should not preclude someone for CAR-T as a treatment option due to concerns of ICANS and bridging with WBRT is not associated with increased ICANS.

Conflict of interest: COI declared - see note

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CAR T-cell Therapy for Secondary CNS DLBCL.
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Secondary CNS Lymphoma, CAR-T, Whole Brain Radiation, Non-Hodgkin Lymphoma, Bridging Therapy.

Key Points:
- Secondary Central Nervous System Lymphoma should not preclude patients from CAR-T cell therapy due to concerns of ICANS
- Whole Brain Radiation is not associated with increased ICANS when used as a bridge to CAR-T cell therapy with short median interval in SCNSL
Abstract:

Management of secondary central nervous system involvement (SCNSL) in relapsed or refractory aggressive B-cell lymphomas remains an area of unmet medical need. We report a single center retrospective analysis of seven adult patients with SCNSL who underwent CAR-T therapy for their refractory disease and describe safety of whole brain radiation as a bridging therapy. Six patients (85.7%) achieved a complete response at D+28, while 1 patient had progressive disease. The median progression free survival was 83 days (28 - 219) and a median overall survival was 129 days (32 - 219). Three patients died due to disease progression. Of the 5 patients who received WBRT as bridging therapy, 3 had no ICANS, while 2 had grade 1 and 3, respectively. No grade 4 ICANS was reported in this subset of patients. We conclude that SCNSL should not preclude someone for CAR-T as a treatment option due to concerns of ICANS and bridging with WBRT is not associated with increased ICANS.
Introduction:

Despite recent advances, the management of secondary central nervous system involvement (SCNSL) in relapsed or refractory aggressive B-cell lymphomas remains an area of unmet medical need since these patients are often excluded from clinical trials.[1, 2] Even among patients with isolated SCNSL, systemic relapse is invariably seen and the median survival of these cases is poor (≤ 6 months). [3-6] The mainstay for treatment for SCNSL remains intravenous high dose methotrexate, whole brain radiation (WBRT) or high dose chemotherapy followed by autologous transplant. New treatment approaches are indicated for these patients. Anti CD-19 chimeric antigen receptor T- cell (CAR-T) therapy is a paradigm changing option for patients with relapsed/refractory diffuse large B-cell Lymphoma (DLBCL), with three Food and Drug Administration (FDA) approved products now available in the United States.[7] The first two registrational CAR-T studies excluded lymphoma patients with CNS involvement due to concerns of Immune effector cell-associated neurotoxicity syndrome (ICANS), but limited retrospective data along with TRANSCEND trial have shown feasibility of CAR-T treatment in SCNSL.[1, 2, 7-10] While in-field systemic radiation has been shown to be safe as a bridging therapy prior to CAR-T, there is no data on safety of WBRT as a bridging therapy prior to CAR-T infusion.[11, 12] Concerns of increased ICANS exist amongst physician groups with combination of both modalities with limited literature to support this. However, mouse models for glioblastoma have shown synergistic effect with combination of CAR-T cells and radiotherapy.[13]

We report here a single center retrospective analysis of seven adult patients with SCNSL who underwent CAR-T therapy for their refractory disease, and also describe safety of WBRT as a bridging therapy in a subset of patients prior to cellular therapy infusion.
Methods:

Patient demographics, disease and CAR-T therapy related variables and patient outcomes were retrieved from the BMT and Cellular Therapy Program Database. Disease and response to treatment assessment were done separately for systemic and central nervous system (CNS) disease. Results from positron emission tomography (PET) scans with Deauville 1, 2 and 3 were considered a complete response (CR), while clearing of lumbar puncture from lymphoma cells (as indicated) and resolution of contrast enhancement within parenchymal lesions on brain magnetic resonance imaging (MRI) were considered a CR for CNS disease. (Supplemental Table S1) Adverse outcomes of cytokine release syndrome (CRS) and ICANS were reported as documented by the primary physicians based on consensus guidelines from American Society of Transplantation and Cellular Therapy for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells.[14] ClonoSEQ® minimal residual disease (MRD) assay from Adaptive Biotechnologies was utilized for assessing MRD status. The study was approved by Medical College of Wisconsin/Froedtert Hospital Institutional Review Board #5 and conducted according to the Declaration of Helsinki.

Results:

Median age was 50 years (range: 39 – 72), and 4 subjects (57.1%) were males. Table 1 describes patient demographics in detail. The median number of prior therapies were 4 (2 - 4) (Detailed regimens in Supplemental Table S1). Median LDH at time of CAR T-cell therapy was 190 unit/L (138 – 327) (Supplemental Table S1). 5 patients had parenchymal involvement while 2 had leptomeningeal disease (LMD). WBRT was administered to 5 of 7 patients at median dose of 2800 cGy (400 - 4000) immediately before their CAR-T as bridging therapy with a lapsed median interval of 21 days (7 - 31) from last fraction of radiation to CAR infusion.
All patients received uniform lymphodepletion with fludarabine and cyclophosphamide. Axicabtagene Ciloleucel (Axi-cel) (n=3) was given at a standard dose of 2 x 10^6 cells/kilogram, while the median number of Tisagenlecleucel (Tisa-cel) (n=4) cells infused were 4 x 10^6 (3 x 10^6 – 4.3 x 10^6). CRS was reported in 4 patients, with Grade 3 or above in only 1 patient. ICANS was reported in 3 of the 7 patients, with all requiring medical interventions. Adverse events and their management are described in Table 1. The median follow-up of survivors is 5.1 months (1.6 – 7.2), and at last follow up 4 patients were alive. Six patients (85.7%) achieved a complete response (CR) at D+28, while 1 patient had progressive disease (PD). The median progression free survival (PFS) was 83 days (28 – 219) and a median overall survival (OS) was 129 days (32 – 219). Three patients died due to disease progression. Of the 5 patients who received WBRT as bridging therapy, 3 had no ICANS, while 2 had grade 1 and 3 respectively. No grade 4 ICANS was reported, and all patients fully recovered with no treatment related mortalities. No patient was taken to transplant after CAR T-cell therapy and no maintenance strategies were employed.

**Discussion:**

SCNSL is associated with poor outcomes and an area for further investigations. [3, 6] ZUMA-1 and JULIET trials which led to CAR-T approval for relapsed refractory DLBCL, excluded patients with CNS involvement due to concerns of increased ICANS. [1, 2] In our patient population, CAR-T therapy appeared to be a safe treatment option in SCNSL with favorable outcomes even among heavily pre-treated patients. Abramson et. al in their letter to editor reported a case of relapsed DLBCL with CNS involvement who received lisocabtagene maraleucel with disease remission at 12-month interval.[9] This led to a case series by Frigault and colleagues of 8 patients with Tisa-cel showing ongoing CR or partial response (PR) at >90 day interval in 3 patients with one at 180 day interval with CR.[7] Bennani et. al also shared their
experience of 17 patients with similar outcomes as compared to patients with no CNS involvement for Axi-cel.[12, 15] TRANSCEND trial included 6 patients with SCNSL of which 3 patients achieved a CR.[10] Our outcomes are consistent with prior reported literature with manageable adverse events and no treatment related mortalities. [7, 16, 17] Our patients had a median OS of 83 days (2.7 months) with 3 patients in complete remission at more than 90-day interval.

Our study is limited by retrospective nature and small sample size but demonstrates two major findings; first that SCNSL should not preclude someone for CAR-T as a treatment option due to concerns of ICANS. Second, we demonstrate that WBRT as a bridging therapy to CAR-T therapy with a short interval (median 21 days) is associated with no new safety signals or increased ICANS, albeit with limited follow-up. It is possible that radiosensitization may improve CAR T-cell outcomes by enhancing T-cell trafficking into the tumor environment which was demonstrated with immunotherapy by Dovedi et. al. Similarly, recent studies have shown improved PFS and overall response rates in patients receiving CAR-T cells with systemic radiation as bridging therapy when compared to chemotherapy. [12, 18, 19] In conclusion, we demonstrate safety of CNS directed radiation as a bridge to CAR-T and provide further evidence that secondary CNS involvement should not preclude CAR-T treatment.

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**Author Contributions:**

G.A., M.H. and N.S. designed research, performed research, analyzed data and wrote the paper. All other authors contributed patients, designed research, critically reviewed and approved the manuscript.

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Conflicts of Interest:

NNS reports receiving honoraria and/or travel support from Incyte, Celgene, Lily, and Miltenyi Biotec; serving on scientific advisory boards for Lily, Kite, Celgene, Legend, Epizyme, Seattle Genetics, and TG therapeutics; equity ownership in Exelixis, Geron; receiving institutional research support for clinical trials Miltenyi Biotec.

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All other authors report no conflicts of Interest.

FIGURE 1 Interval from Last WBRT to CAR-T and PFS.
Legend: Solid Black Line = Median Days from Last WBRT to CAR-T (21 days), Solid Green Line = Median Progression Free Survival (83 days). WBRT= Whole Brain Radiation, PFS = Progression Free Survival of patients who were bridged with WBRT. Symbol → - on going complete response, Symbol ↓ - relapsed
Table 1. Demographics, Outcomes and Management of Adverse events

| ID | Age, Sex | Disease Location | Systemic Disease at CAR-T | Prior Lines of therapy | Prior Auto HCT | Bridging WBRT, Total Dose, Fractions | Pre-CAR Systemic Status | Product | D+28 Systemic Response | D+ 28 CNS Status (Assessment study) | MRD Status at D+28 | CRS, Grade, Treatment | ICANS and Grade | Treatment of ICANS | Relapse Y/N | Current Status |
|----|----------|------------------|---------------------------|------------------------|----------------|--------------------------------------|------------------------|---------|-----------------------|-----------------------------|------------------|------------------|------------------|-------------------|------------|-----------------|
| 1  | 47, M    | LMD              | Yes                       | 4                      | Yes            | No                                   | CR                     | Axi-cel | CR                   | CR                         | Negative | Yes, 1 Tocilizumab | No              | N/A               | No, Day 91+   | Alive with CR at Day 91+ |
| 2  | 72, F    | Parenchyma       | No                        | 4                      | No             | Yes, 2800 cGy, 14                    | PD                     | Axi-cel | CR                   | CR                         | Negative | Yes, 1, None      | Yes, 3          | Solumedrol pulse and Dexamethasone taper | No, Day 129+ | Alive with CR at Day 129+ |
| 3  | 42, F    | Parenchyma       | No                        | 4                      | No             | Yes, 2340 cGy, 13                    | CR                     | Tisa-cel | CR                   | CR                         | N/A             | Yes, 3, Tocilizumab and dexamethasone taper | Yes, 1          | Dexamethasone Taper | No, Day 219+ | Alive with CR at Day 219+ |
| 4  | 39, F    | LMD              | Yes                       | 2                      | No             | No                                   | PD                     | Axi-cel | CR                   | N/A                         |                | Yes, 2, Tocilizumab and dexamethasone taper | Yes, 2          | Dead due to PD Day 109 |
| 5  | 50, M    | Parenchyma       | No                        | 4                      | Yes            | Yes, 4000 cGy, 20                    | PD                     | Tisa-cel | CR                   | CR                         | Negative | No               | No              | N/A               | Yes, Day 83   | Dead, due to PD Day 133 |
| 6  | 72, M    | Parenchyma       | No                        | 2                      | No             | Yes, 400 cGy, 2                       | PD                     | Tisa-cel | PD                   | N/A                         | No             | No               | No              | N/A               | Yes, Day 28   | Dead due to PD Day 63 |
| 7  | 51, M    | Parenchyma       | Yes                       | 3                      | No             | Yes, 3000 cGy, 18                    | PD                     | Tisa-cel | CR                   | CR                         | Negative | No               | No              | No                | No, Day 48+   | Alive with CR at Day 48+ |
M = Male, F = Female, LMD = Leptomeningeal Disease, LP = lumbar puncture, Auto HCT = Autologous Hematopoietic Cell Transplant, WBRT = Whole Brain Radiation, cGy = Centigray, CR = complete response, PR = Partial Response, PD = Progressive Disease, SD = stable disease, N/A = Not applicable/available. Patients who received WBRT are in bold.

*Had PD before CAR-T cell infusion, got 2 Gy x 2 of Whole Brain Radiation and response assessed after D+28
**Figure 1:** Interval from Last WBRT to CAR-T and PFS

Legend: Solid Black Line = Median Days from Last WBRT to CAR-T (21 days), Solid Green Line = Median Progression Free Survival (83 days). WBRT = Whole Brain Radiation, PFS = Progression Free Survival of patients who were bridged with WBRT. Symbol $\rightarrow$ - on going complete response, Symbol $\downarrow$ - relapsed