REGULAR ARTICLE

blood advances

CNS bridging radiotherapy achieves rapid cytoreduction before CAR T-cell therapy for aggressive B-cell lymphomas

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Key Points

- Bridging radiotherapy (BRT) for chemotherapy-refractory CNS lymphoma achieves rapid cytoreduction before CART.
- CNS-BRT is associated with a favorable CNS response profile and CART–associated neurotoxicity profile.

Chimeric antigen receptor (CAR) T-cell therapy (CART) for central nervous system lymphoma (CNSL) is a promising strategy, yet responses are frequently not durable. Bridging radiotherapy (BRT) is used for extracranial lymphoma in which it can improve CART outcomes through cytoreduction of high-risk lesions. We hypothesized that BRT would achieve similar, significant cytoreduction before CART for CNSL (CNS-BRT). We identified patients with CNSL with non-Hodgkin B-cell lymphoma who received CNS-BRT before commercial CART. Cytoreduction from CNS-BRT was calculated as change in lesion size before CART. Twelve patients received CNS-BRT, and the median follow-up among survivors is 11.8 months (interquartile range, 8.5-21.9). Ten patients had CNSL (9 secondary, 1 primary) and 2 patients had epidural disease (evaluable for toxicity). All 10 patients with CNSL had progressive disease at the time of CNS-BRT. Of 12 patients, 1 experienced grade ≥3 cytokine release syndrome, and 3 of 12 patients experienced grade ≥3 immune effector cell–associated neurotoxicity syndrome. CNS-BRT achieved a 74.0% (95% confidence interval, 62.0-86.0) mean reduction in lesion size from baseline (P = .014) at a median of 12 days from BRT completion and before CART infusion. Best CNS response included 8 complete responses, 1 partial response, and 1 progressive disease. Three patients experienced CNS relapse outside the BRT field. Preliminary data suggest CNS-BRT achieves rapid cytoreduction and is associated with a favorable CNS response and safety profile. These data support further study of BRT as a bridging modality for CNSL CART.

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Pertinent data will be shared upon reasonable request via email to the corresponding author, Brandon S. Imber (imberb@mskcc.org).

The full-text version of this article contains a data supplement.

Introduction

Primary and secondary central nervous system lymphoma (CNSL) are rare, aggressive manifestations of non-Hodgkin lymphoma (NHL). CD19 chimeric antigen receptor T-cell therapy (CART) has revolutionized the treatment of extracranial NHL with emerging but promising response signals for CNSL.[1-6] However, concerns about the durability of response after CART[7,8] suggest that additional strategies to maximize CNS control are warranted. Moreover, ~80% of patients receiving CART require bridging therapy because of symptomatic or rapidly progressing disease,[1,4,9] yet few data exist to guide optimal CNS bridging strategy.[10]

Radiotherapy is a promising CART bridging strategy for CNSL for multiple reasons. First, bridging radiotherapy (BRT) for extracranial lymphoma is safe, has rapid cytoreductive power, and appears to reduce relapse risk in irradiated high-risk sites.[11-14] Second, salvage radiotherapy for recurrent or refractory CNSL is associated with high response rates of 67% to 88%.[15,16] Third, BRT avoids systemic toxicity associated with chemotherapy, which can hinder subsequent receipt of CART.[10] Fourth, BRT may enhance CART efficacy by preventing antigen escape.[17]

Despite compelling rationale, specific concerns about CNS-directed BRT (CNS-BRT) remain, given the potential for excess neurotoxicity. CART–associated neurotoxicity is driven by endothelial activation, blood-brain barrier disruption, monocyte dysregulation, cytokine release, and tumor inflammation.[18-21] Given that radiotherapy can lead to enhanced permeability of the blood–brain barrier and augment local inflammation,[22,23] CNS-BRT has a theoretical potential to enhance CART neurotoxicity. We report our experience of safety, response, and relapse pattern after CNS-BRT before CART.

Methods

Patient cohort

We included all consecutively treated patients with pathologically confirmed NHL involving the CNS who received BRT at the Memorial Sloan Kettering Cancer Center in the period spanning 30 days before leukapheresis through commercial CAR T-cell infusion between 2019 and 2023, to ensure a minimum follow-up of 6 months. CNS involvement included disease infiltration of the brain or spinal cord parenchyma or leptomeningeal space. We also included patients with significant epidural involvement for relevant toxicity assessment because the BRT field would encompass the adjacent spinal cord.

CNSL-directed therapy was defined as systemic therapy prescribed for a known diagnosis of CNSL, as opposed to prophylaxis before demonstrated CNS disease. Systemic therapy was defined as concurrent if there was any overlap with BRT, that is, systemic therapy and BRT were administered at least once on the same day. This research was approved by the Memorial Sloan Kettering Cancer institutional review board. All patients provided signed informed consent for treatment with immune effector cells.

CNS-BRT

CNS-BRT was delivered using intensity modulated radiotherapy or conventional techniques. Whole-brain radiotherapy fields were treated with standard opposed fields to the inferior C2 vertebra. Partial brain radiotherapy fields encompassed a radiographically defined clinical target volume (CTV) with a 3-mm to 10-mm geometric expansion for the planning target volume. For intact tumors, the CTV was defined as radiographically visible disease with up to 5-mm expansion to account for possible microscopic spread. Involved site spine fields generally encompassed a radiographically defined CTV with 1.5- to 3-cm superior and inferior margin to field edge using conventional planning.

Outcome assessment

Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded by an institutional multidisciplinary conference according to the American Society of Transplantation and Cellular Therapies consensus criteria[24] for 11 of 12 patients; 1 patient received CART at an outside institution and toxicity was graded per outside physician report. Immune effector cell encephalopathy (ICE) scores were graded per physician report. Additional CNS-BRT–related toxicities were graded according to Common Terminology Criteria for Adverse Events version 5.0.

CNS response to BRT and subsequent relapse were evaluated for patients with CNSL but not for patients who received CNS-BRT for purely epidural lesions. CNS response of parenchymal and leptomeningeal lesions were evaluated on postcontrast magnetic resonance imaging (MRI). Response evaluations were performed by an expert CART review committee and an independent, experienced blinded neuro-oncology radiologist (J.S.) to achieve clinical consensus. Evaluated lesions were identified on postcontrast MRI on the series with the thinnest slice thickness using the plane in which the lesion had the greatest long axis diameter. Total lesion size was defined as the sum of product diameters for all measurable lesions. The product diameter is the longest axis diameter multiplied by the orthogonal diameter for a single lesion; this value is calculated for each lesion and summed together. For response and relapse evaluation, comparisons were done in the same imaging plane. Spinal intramedullary disease was defined as involvement of soft tissue structures within the thecal sac. Complete response (CR) was defined as disappearance of all contrast enhancing tumor; small residual areas of contrast enhancement could be considered CR if they demonstrated stability on multiple longitudinal scans in the absence of further therapy. Patients with evidence of leptomeningeal disease at the time of BRT must have also had documented negative cerebrospinal fluid (CSF) cytology to be considered in CR. Partial response (PR) was defined as at least a 50% reduction in the size of contrast enhancing tumor, without the development of any new tumors. Progressive disease (PD) was defined as growth of contrast-enhancing tumor by >25% or the development of any new tumors. Stable disease included tumors that did not achieve PR and did not show evidence of PD. CNS relapse was defined as PD within the CNS parenchyma or leptomeninges. Cytoreduction due to BRT was calculated by determining the change in total lesion size at pre-BRT baseline compared with after BRT but before CAR T-cell infusion. Patients were excluded from cytoreduction analysis if they did not undergo interim MRI between the end of CNS-BRT and CAR T-cell infusion.

Statistical analysis

Patient and treatment characteristics are reported as median and range for continuous variables and counts for categorical variables. The cumulative incidence of CNS relapse measured from CAR T-cell infusion was calculated by cumulative incidence functions assuming death as a competing risk, reported with 95% confidence intervals (CIs). Follow-up time among survivors was estimated using the reverse Kaplan-Meier method. Significance for quantitative cytoreduction was calculated using a paired sample *t* test, and the association between CNS tumor size by high-grade ICANS (grade ≥3) using an unpaired 2-sided *t* test. Statistical significance was set at $P < .05$ and performed using Graphpad Prism (version 9.3.1, GraphPad Software) and R Studio (version 4.1.2, R Foundation for Statistical Computing).[25]

Results

Patient demographics and clinical characteristics

We identified 12 eligible patients who received CNS-BRT before CART (Table 1). Median follow-up among survivors was 11.8 months (interquartile range, 8.5-21.9). Diagnoses included diffuse large B-cell lymphoma (n = 8), mantle cell lymphoma (n = 2), Burkitt lymphoma (n = 1), and primary CNS lymphoma/diffuse large B-cell lymphoma (n = 1). Involved CNS sites included brain parenchyma (n = 6), leptomeninges (n = 4), and spinal epidural space (n = 2). Five patients had concomitant systemic disease at the time of CNS-BRT. Median age at CNS-BRT was 60 years (range, 30-76), and median Karnofsky Performance Status was 80 (range, 50-90). Nine patients were symptomatic from their CNS disease at the time of CNS-BRT. The median number of prior CNSL-directed therapies was 2 (range, 0-4). Nine patients received prior high-dose methotrexate (HD-MTX) with a median time of 46 days between the last HD-MTX infusion and the start of CNS-BRT (range, 0-393). Five patients had received prior autologous hematopoietic stem cell transplantation.

CNS-BRT characteristics

All 10 patients with CNSL (parenchymal and leptomeningeal involvement) had progressive CNS disease at the time of CNS-BRT. Of 2 patients with epidural disease, 1 patient had PD whereas the other had radiographically stable but symptomatic lymphoma. CNS-BRT fields included whole brain (n = 3), involved site "partial" brain (n = 4), involved site spine (n = 4), and orbits (n = 1). The median treatment dose was 22 Gy[15-33] in 10 fractions.[5-12] Seven patients received systemic therapy as part of bridging, in addition to CNS-BRT; systemic therapy bridging included MTX (HD-MTX [n = 4], intrathecal-MTX [n = 1], rituximab [n = 2], ibrutinib [n = 2], cytarabine [n = 1], pembrolizumab [n = 1], and venetoclax [n = 1]). Four patients progressed on systemic therapy bridging before initiation of CNS-BRT. In general, cytotoxic chemotherapy and CNS-BRT were given sequentially. However, 1 patient initiated CNS-BRT concomitantly with the last dose of HD-MTX because of progressive symptoms. Ibrutinib (n = 2) and venetoclax (n = 1) were given concurrently with CNS-BRT.

Median time from apheresis to CAR T-cell infusion was 66 days (range, 25-199). Median time from CNS-BRT completion to CAR T-cell infusion was 20 days (range, 10-212). Ten patients received fludarabine/cyclophosphamide lymphodepleting therapy, and 2

Table 1. Patient characteristics

Patient	Age at BRT (y)	Length of follow-up (mo)	Sex	Histology	Prior ASCT	CNS prophylaxis	Prior lines of CNS therapy	HD-MTX	Interval MTX to RT (days)	CNS disease status at RT	Systemic disease status at RT	KPS at RT	CNS site involved	RT field	RT dose (cGy)	RT fractions	Concurrent systemic therapy with RT	Preparative regimen	Apheresis to infusion time (d)	CART product	Baseline ICE	ICANS	ICANS duration	CRS	CRS duration	Requiring biologics or steroids?	Best CNS response post CART	Best overall response post CART	Status at last follow up
1	60	5.7	Male	Mantle cell	No	No	4	No		PD	PD	80	Leptomeninges	Orbits	1500	10	Venetoclax	Cy/Flu	70	Liso-cel	Not available	0	0	0	0	None	CR	PD	Dead
2v	36	5.7	Female	Burkitt	Yes	Yes	2	Yes	0	PD	ND	80	Leptomeninges	Whole brain	2000	5	HD-MTX	Cy/Flu	25	Tisa-cel	Not available	1	Not available	0	0	None	CR	PR	Dead
3	74	3.3	Female	DLBCL	No	No	2	Yes	21	PD	SD	60	Leptomeninges	T11-L3	2000	5	Ibrutinib	Cy/Flu	63	Tisa-cel	5	3	25	3	2	Tocilizumab	PD	PD	Dead
4	70	10.1	Male	Mantle cell	Yes	No	0	No		N/A	PD	90	Epidural	T8 - L1	2000	5	None	Cy/Flu	81	Liso-cel	10	0	0	1	5	None	N/A	CR	Dead
5	66	33.1	Male	DLBCL	No	No	2	Yes	174	PD	ND	90	Brain parenchyma	Partial brain	3000	10	None	Cy/Flu	45	Tisa-cel	10	0	0	0	0	None	CR	PD	Alive
6	41	23.0	Female	PCNSL	Yes	No	4	Yes	62	PD	N/A	80	Brain parenchyma	Whole brain	2400	12	None	Cy/Flu	54	Tisa-cel	10	0	0	2	5	None	CR	CR	Alive
7	48	11.4	Female	DLBCL	No	No	2	Yes	179	PD	ND	50	Brain parenchyma	Whole brain	2400	12	None	Cy/Flu	69	Liso-cel	6	4	Not available	2	4	Tocilizumab, anakinra, steroids, IVIG	PR	PR	Dead
8	51	12.6	Male	DLBCL	No	No	0	No		N/A	SD	90	Epidural	C5-C7, sacrum	2000	5	None	Bendamustine	28	Axi-cel	10	0	0	2	7	Tocilizumab, steroids	N/A	PR	Alive
9	30	11.9	Female	DLBCL	Yes	No	3	Yes	46	PD	ND	90	Brain parenchyma	Partial brain	3300	11	None	Cy/Flu	61	Liso-cel	10	4	7	1	3	Tocilizumab	CR	CR	Alive
10	61	15.6	Male	DLBCL	Yes	Yes	2	Yes	393	PD	ND	80	Leptomeninges	Cauda	2000	5	Ibrutinib	Cy/Flu	199	Liso-cel	10	0	0	1	1	Tocilizumab, steroids	CR	CR	Alive
11	71	8.3	Male	DLBCL	No	No	2	Yes	32	PD	PD	60	Brain parenchyma	Partial brain	3000	10	None	Bendamustine	68	Liso-cel	10	2	15	2	6	Tocilizumab, anakinra, steroids	CR	CR	Alive
12	76	6.9	Female	DLBCL	No	No	3	Yes	9	PD	ND	90	Brain parenchyma	Partial brain	3000	10	None	Cy/Flu	129	Liso-cel	10	0	0	0	0	None	CR	CR	Alive

Summary of demographic, clinical, treatment, and toxicity characteristics for 12 patients.
ASCT, autologous stem cell transplant; Axi-cel, axicabtagene ciloleucel; cGy, centigray; Cy, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; Flu, fludarabine; IVIG, IV immunoglobulin; KPS, Karnofsky Performance Status; Liso-cel, Lisocabtagene maraleucel; N/A, not applicable; ND, no disease; PCNSL, primary central nervous sytem lymphoma; RT, radiotherapy; SD, stable disease; Tisa-cel, tisagenlecleucel.

received bendamustine. CART products included lisocabtagene maraleucel (n = 7), tisagenlecleucel (n = 4), and axicabtagene ciloleucel (n = 1).

Toxicity associated with CNS-BRT and subsequent CART

Eight patients (75%) experienced mild toxicities possibly attributable to CNS-BRT, all of which were grade ≤2. Toxicities that occurred in >1 patient included fatigue (n = 6 grade 1, n = 1 grade 2), dermatitis (n = 2 grade 1), and cognitive disturbance (n = 1 grade 1, n = 1 grade 2). Toxicities that were observed once included grade 1 headache and grade 1 depressed level of consciousness. No toxicities of grade ≥3 were observed.

After CAR T-cell infusion, 8 of 12 patients (75%) experienced CRS; most events were grade ≤2 (grade 1 [n = 3], grade 2 [n = 4]). One patient experienced grade 3 CRS. Five of 12 patients (42%) experienced ICANS, 3 of whom experienced high-grade ICANS (grade 3 [n = 1], grade 4 [n = 2]). Two of the high-grade cases were reversible (Table 1). All patients were on seizure prophylaxis. The 3 patients who developed severe ICANS had impaired neurologic function at baseline, which was likely multifactorial with contributions from CNSL and other factors. Patient 3 had baseline Karnofsky Performance Status of 50 to 60; ICE score of 5; and intermittent confusion, hallucinations, and disorientation to place. After CAR T-cell infusion, she developed severe encephalopathy requiring intubation, however the syndrome was transient and neurologic status recovered to baseline. Patient 7's baseline ICE score of 6 and neurologic assessment was "awake, but not alert" with intermittent confusion, aphasia, and documented focal seizure. The patient developed grade 4 ICANS with seizures, communicating hydrocephalus, altered mental status, and myelitis that was irreversible. Patient 9 had grade 4 ICANS characterized by seizure activity 16 days after CAR T-cell infusion, which was reversible. This patient had known baseline epilepsy and the seizure she experienced after CART was of the same semiology as her prior seizures and occurred in the setting of an acute viral infection. There was a trend toward larger CNS tumor size in patients who experienced high-grade ICANS, however this difference was not statistically significant (supplemental Figure 1). Overall, 6 patients received both tocilizumab and steroids.

Cytoreduction from CNS-BRT before CART therapy

Of 10 efficacy-evaluable patients, 8 had imaging before and after CNS-BRT and were evaluable for quantitative cytoreduction. Median time from the end of CNS-BRT to the radiographic assessment was 12 days (range, 2-55). Of 8 patients, 3 were on steroids at the time of radiographic assessment. Among 8 evaluable patients, CNS-BRT produced a significant reduction in lesion size ($P = .014$). All 8 patients had at least a PR without any progressing lesions. The mean reduction in lesion size was 74% (95% CI, 62-86; Figure 1A). Both leptomeningeal and brain parenchymal lesions responded well to CNS-BRT (Figure 1B-C).

Overall response

The best overall response after CART included n = 6 CR, n = 3 PR, and n = 3 PD. Best CNS response after CAR T-cell infusion included n = 8 CR, n = 1 PR, and n = 1 PD (Figure 2A). The best CNS response after CNS-BRT, which was defined as the maximal decrease in lesion size at any point after CNS-BRT or CAR T-cell infusion, included n = 8 CR and n = 2 PR; that is, 1 patient had a PR after CNS-BRT but developed out-of-field CNS recurrent disease before CART and continued to have further CNS progression after CART. The median time to best CNS response was 170 days (range, 31-307). The mean maximal change in lesion size was −94.8% (95% CI, −89.4 to −100.1; Figure 2B).

CNS relapse

Among the CNSL cohort (n = 10), there were no in-field CNS recurrences. The 12-month cumulative risk of any CNS relapse was 25% (95% CI, 6-52), which included 3 relapse and/or progression events (Figure 3A). Of note, the 3 relapse/progression events occurred in patients with active or prior leptomeningeal disease. Patient 1 had radiographic leptomeningeal involvement of the V1 nerve and positive CSF cytology at the time of CNS-BRT. This patient received CNS-BRT to a bilateral orbital field to target the radiographic disease, as well as additional systemic bridging therapy (rituximab, cytarabine, and venetoclax); CSF cytology cleared before CART. He experienced an out-of-field recurrence in the brain 1 month after CAR T-cell infusion. Patient 3 had a bulky lumbar leptomeningeal tumor and positive CSF cytology at the time of CNS-BRT. This patient received CNS-BRT to the lumbar lesion with concurrent ibrutinib. After initial response, she developed a multifocal leptomeningeal recurrence, including at the margin of the prior RT field, before CART. She experienced further progression after CAR T-cell. Patient 12 had a history of positive CSF cytology, but this was negative at the time of CNS-BRT. She received CNS-BRT to a progressive right basal ganglia lesion and ultimately had a periventricular recurrence at the margin of the prior radiotherapy field (Figure 3B).

Discussion

We report a retrospective series of patients who received CNS-BRT for NHL, including 10 patients with CNSL (1 primary CNSL [PCNSL], 9 secondary CNSL [SCNSL]) and 2 patients who received CNS-BRT to epidural targets. This represents a particularly high-risk and difficult-to-manage cohort because all 10 patients with CNSL had CNS disease progressive through standard chemotherapy, and 11 of 12 patients in the cohort had PD at the time of CNS-BRT. Importantly, CNS-BRT achieved significant cytoreduction of all treated lesions, at a median interval of only 12 days from the completion of BRT. This rapid and robust response is critical as it demonstrates that BRT can achieve tumor control and potentially symptom palliation within the often-narrow timeframe of the CART bridging period. This response was maintained or improved after CART for 9 of 10 patients, at least temporarily. Only 1 patient did not respond to CART and exhibited rapidly progressive leptomeningeal disease, which was fatal. The 12-month estimated risk of CNS relapse and/or progression after CART was 25%, in this limited and heterogeneous cohort.

The overall rate of CRS in this study was 67% (8/12) and high-grade CRS was 8% (1/12). The overall rate of ICANS was 42% (5/12) and 25% high-grade (3/12). The overall rate of toxicity reported here is largely similar to what is reported in the literature for patients with CNSL. A series of 10 patients with active SCNSL treated with CART reported that 3 of 10 patient developed high-grade ICANS and this was not associated with radiotherapy.[26] In

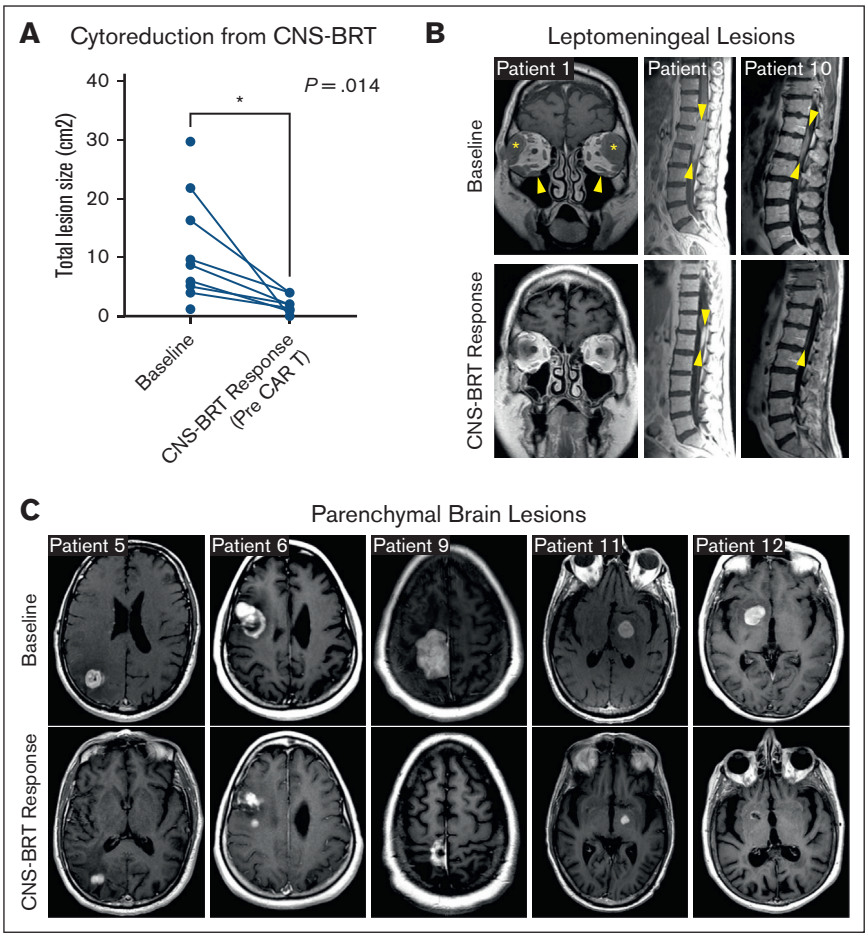

Figure 1. CNS-BRT response. (A) Paired lesion-size analysis shows a significant decrease in lesion size after CNS-BRT, before CAR T-cell infusion ($P = .014$). The mean decrease in lesion size was 74.8%. (B) Baseline imaging and CNS-BRT response for patients with leptomeningeal lesions. Patient 1: coronal T1 postcontrast MRI through orbits shows disease centered in bilateral superolateral extraconal fat (asterisks) and infiltrating the bilateral infraorbital nerves (arrowheads); 55 days after radiotherapy (RT) completion there is near complete resolution of orbital masses and decreased prominence of the infraorbital nerves. Patient 3: sagittal T1 postcontrast MRI of the lumbar spine demonstrating enhancing soft tissue mass filling much of the thecal sac from T12-L2; 19 days after RT completion there is marked decrease in intrathecal contrast enhancement (arrowheads). Patient 10: sagittal T1 postcontrast MRI of the lumbar spine showing enhancing soft tissue mass filling much of the thecal sac from T12 to superior extent of L2; 43 days after RT completion there is near complete resolution of the mass (arrowheads). Patient 3 and 10 had bulky spinal leptomeningeal lesions. (C) Baseline imaging and CNS-BRT response for patients with parenchymal brain lesions. All images show axial T1 postcontrast MRIs of the brain. Patient 5: enhancing lesion centered in the right occipital lobe shows significant reduction in size 2 days after RT completion. Patient 6: enhancing right frontal/operculum lesion shows significant reduction in size, 3 days after RT completion. Patient 9: enhancing paramedian lesion at the right frontoparietal convexity shows marked reduction in size, 42 days after RT completion. Patient 11: enhancing lesion centered in the left thalamus shows significant contraction, 4 days after RT completion. Patient 12: enhancing right gangliocapsular lesion shows near complete resolution, 5 days after RT completion.

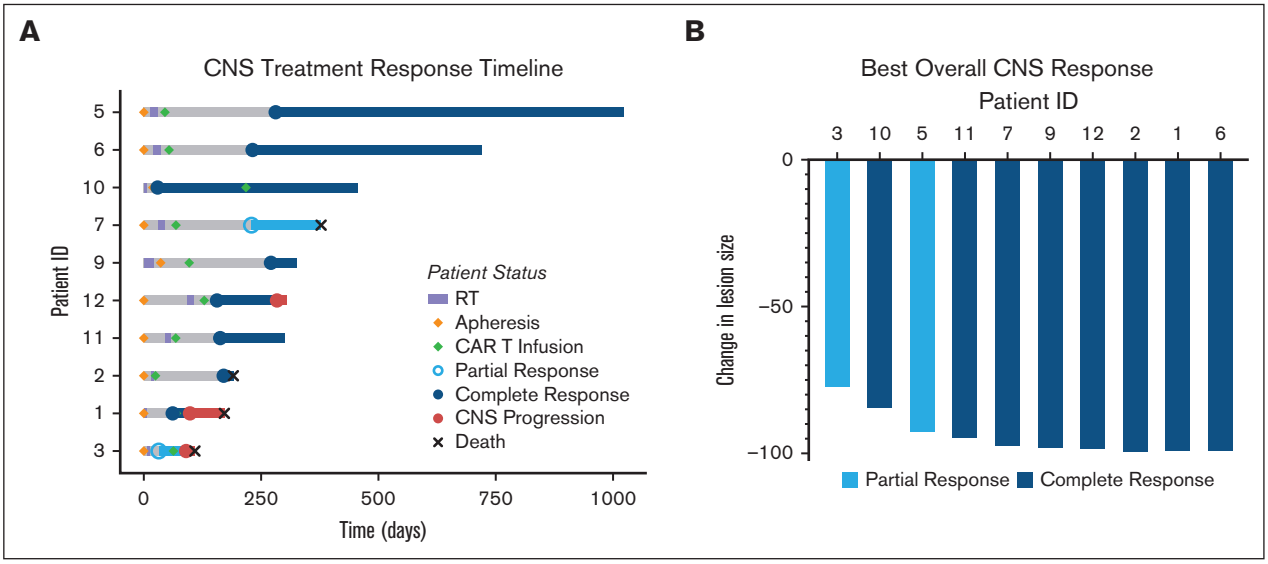

Figure 2. CNS response. (A) Swimmers plot of treatment, response, and relapse time for 10 patients with CNSL. Status and events are coded in the legend. Response times on the plot correspond to the time when the best response was achieved. (B). Waterfall plot showing the best overall CNS response as measured by change in lesion size (sum of product diameters) from baseline. All 10 patients exhibited a response. The mean best response was a decrease in lesion size by 94.8% (95% CI, −89.4 to −100.1). Overall, there were 8 CRs and 2 PRs.

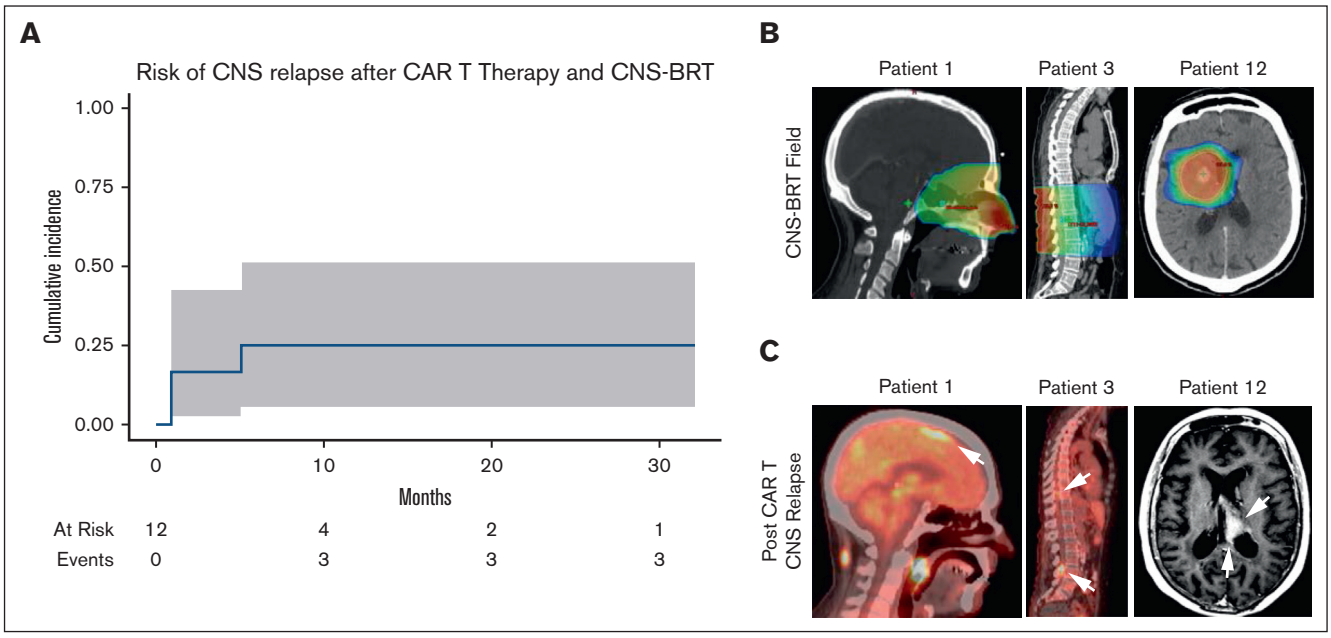

Figure 3. CNS relapse. (A) The 12-month cumulative risk of CNS relapse after CNS-BRT and CART was 25.0% (95% CI, 6-52). (B) Images showing the CNS-BRT treatment plans to the 50% isodose line. Patient 1: sagittal postcontrast computed tomography (CT) of the head with RT field targeting the orbits. Patient 3: sagittal noncontrast CT of the spine with RT field targeting T11 through L3. Patient 12: axial noncontrast CT of the head with RT field targeting the right gangliocapsular area. (C) Images show sites of post-CART CNS relapse. Patient 1: sagittal positron emission tomography (PET)/CT showing [^{18}F]fluorodeoxyglucose (FDG)-avid relapse in the brain, 1 month after CAR T-cell infusion (white arrow). Patient 3: sagittal PET/CT showing 2 FDG-avid sites of relapse at the margins of prior RT field, 1 month after CAR T-cell infusion (white arrows). Patient 12: axial postcontrast T1 MRI showing a left periventricular relapse, 5 months after CAR T-cell infusion (white arrows).

a meta-analysis, Cook et al examined 128 patients who received CART for CNSL and reported composite CRS rates of 70% for PCNSL (13% high grade) and 72% for SCNSL (11% high grade). They report a 53% rate of ICANS for PCNSL (18% high grade) and 48% rate of ICANS for SCNSL (26% high grade).[1] Epperla et al performed a multicenter retrospective analysis of 61 patients who received CART for SCNSL and reported a 44% risk of high grade ICANS; this was also not associated with the receipt of BRT.[27] In combination, our early data support the notion that CNS-BRT is not clearly associated with excess neurotoxicity,[2] although larger series and prospective validation is required. We acknowledge that only 1 patient in our cohort was treated with axicabtagene, whereas ~40% of patients in the referenced cohorts received axicabtagene[1,27]; axicabtagene is known to have greater ICANS risk versus 4-1BB products.[28-31]

Two patients who experienced severe ICANS in our cohort had impaired baseline neurologic function with decreased ICE scores of 5 and 6 before CAR T-cell infusion, which likely predisposed to CART–associated neurotoxicity. Overall tumor burden has previously been shown to correlate with CART–associated neurotoxicity.[32] Patients who developed severe ICANS in our cohort had a numerically larger tumor size at baseline and after CNS-BRT, however this difference was not statistically different. A larger cohort will be needed to determine whether the radiomics of active CNS disease at the time of CART is correlated with the neurotoxicity risk or severity.

At present, given the relatively paucity of data, it may be advisable to use CAR T-cell products with favorable toxicity profile, such as the 4-1BB products, when planning to integrate CNS-BRT. If clinically feasible, CNS-BRT should not be given concurrently with cytotoxic chemotherapy given historical concerns for enhanced toxicity. Combined modality bridging that incorporates CNS-BRT and other systemic agents such as targeted therapies is an interesting avenue to explore but awaits data on safety and tolerability.

There is now an emerging body of literature that suggests that BRT for extracranial lymphoma is associated with better response to CART through rapid cytoreduction and reduced relapse of high-risk lesions.[13,14,33] The data here provide early evidence that, similar to that for extracranial sites, BRT can achieve critical cytoreduction for CNS lesions. Consistent with the notion that BRT can reduce relapse at high-risk sites, there were no in-field, local relapses observed in this series.

All 3 relapses that occurred in this study were associated with either active or former leptomeningeal disease. It is likely that leptomeningeal involvement confers greater risk for CNS relapse after BRT, with prior studies showing that leptomeningeal involvement is associated with poorer outcomes for patients with CNSL treated with radiotherapy.[16] This is not surprising because radiotherapy is typically a focal treatment, whereas leptomeningeal disease is a diffuse process that involves the entire neuroaxis. In the future it may be interesting to explore alternative bridging strategies to optimize control of leptomeningeal disease. For example, very low–dose radiation (4 Gy) has been shown to augment CART tumor killing via death-receptor signaling augmentation; this very low–dose radiation is also associated with minimal toxicity in a large randomized phase 3 study.[17,34] Very low–dose bridging radiation to the craniospinal axis may improve tumor control in the leptomeningeal compartment after CART.

Limitations of this study include the small sample size and retrospective nature. This is in large part because of the rare nature of CNSL. As such, the cohort has heterogeneity of lymphoma histology and CAR T-cell product. The study does not contain a comparator arm of patients who did not receive CNS-BRT. It is challenging to find an appropriate comparator group because this is a selected cohort that typically received CNS-BRT out of necessity after progressing on CNS-directed systemic therapy. Despite these limitations the effect of CNS-BRT on tumor response was consistent across all patients examined.

In the future, it will be important to determine the lesion level characteristics that are associated with CNS relapse so that it may be possible to determine which patients stand to benefit from CNS-BRT. These studies should assess whether CNS-BRT alters the immune effector cell–toxicity profile, optimal timing of CNS-BRT, and whether CNS-BRT improves the overall response and durability of CNS–directed CART. Practically speaking, the successful implementation of a combined modality approach requires significant coordination between medical oncology, cellular therapy, and radiation oncology teams. Overall, this study provides early evidence that CNS-BRT can be an important option in the CART bridging toolbox, especially for CNSL for which the options for bridging therapy may otherwise be limited.

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Authorship

Contribution: G.Y.C., J.Y., and B.S.I. designed research; G.Y.C., S.M.D., and B.S.I. analyzed data; G.Y.C., J.S., and C.G. evaluated neuroradiologic response; G.L.S., R.S., P.B.D., R.J.L., M.-A.P., M.L.P., M.S., and C.G. evaluated clinical response and toxicity; G.S., R.S., H.H., K.T., A.A.T., B.F., C.H., A.B., A.L.D.A., M.C., G.C., P.B.D., R.J.L., P.G., G.S., M.-A.P., M.L.P., L.F., M.S., C.G., and J.Y. discussed results and edited the manuscript; and G.Y.C. and B.S.I. wrote the manuscript, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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