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Clinical Investigation

Radiation Therapy as an Effective Salvage Strategy for Secondary CNS Lymphoma

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Summary

We reviewed the outcomes of patients with secondary central nervous system involvement by diffuse large B-cell lymphoma who were treated with radiation therapy (RT) at a single institution. RT was associated with high rates of radiographic disease response and local control. Overall survival was superior in patients who achieved a complete or partial response to RT, who underwent autologous stem cell transplantation after RT, and who had brain parenchymal (vs leptomeningeal) disease.

Purpose: We assessed the efficacy of radiation therapy (RT) in the management of secondary central nervous system (CNS) lymphoma.

Methods and Materials: The cohort comprised 44 patients with systemic diffuse large B-cell lymphoma (DLBCL) secondarily involving the brain and/or leptomeninges at initial diagnosis or relapse that was treated with RT.

Results: Of these patients, 29 (66%) were in systemic remission when CNS disease was diagnosed. The overall response rate to RT by magnetic resonance imaging was 88% (42% complete, 46% partial). The median overall survival (OS) after RT initiation was 7 months (95% confidence interval 4-10 months). The OS curve plateaued at 31% from 2 to 8 years. OS was superior in patients who achieved a complete or partial response to RT, underwent stem cell transplantation after RT, and had brain parenchymal (vs leptomeningeal) disease. Eight cases of CNS disease progression occurred after RT: 1 involved the brain parenchyma, and 7 involved the spine and/or cerebrospinal fluid and/or meninges.

Conclusions: We conclude that RT is associated with high response rates and may contribute to long-term OS. In addition, RT may provide CNS disease control that facilitates successful salvage with stem cell transplantation in patients with chemotherapy-refractory disease.

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Introduction

Systemic diffuse large B-cell lymphoma (DLBCL) with secondary involvement of the central nervous system (CNS) is uncommon, with a reported cumulative incidence of approximately 5% (1-5). Historically, secondary CNS lymphoma (SCNSL) was almost uniformly fatal (1, 2). However, progress in the management of these patients has resulted in improved outcomes. Most recent protocols consist of high-dose methotrexate (MTX)—based induction therapy, followed by CNS-penetrating regimens given as part of autologous stem cell transplantation (SCT). This approach has resulted in favorable results, particularly in patients who achieve a complete response (CR) to induction chemotherapy. Impressive 2-year overall survival (OS) rates of 51% to 68% have been reported in phase 2 trials (6-8). However, in practice, only a minority of patients may be candidates for this management strategy, because of either inadequate performance status or poor disease response to induction chemotherapy (9). In such cases, radiation therapy (RT) may be a valuable alternative or adjunct to other CNS-directed therapy.

Data regarding clinical outcomes after RT for SCNSL are limited. One retrospective study reported on the use of salvage RT for CNS lymphoma that was refractory to or recurrent after MTX (10); however, this cohort was heterogeneous. We evaluated a more homogeneous population comprising 44 patients with DLBCL secondarily involving the brain and/or leptomeninges that was treated with RT. Our primary objective was to assess radiographic disease response and OS rates. In addition, we analyzed factors associated with successful salvage.

Methods and Materials

Patients

After obtaining institutional review board approval, we identified patients with systemic DLBCL secondarily involving the brain and/or leptomeninges at initial diagnosis or relapse who received RT targeting the brain at our institution from 2006 to 2016. To create a more homogeneous cohort, patients with isolated orbital or spinal disease were not included.

Endpoints

The primary endpoints were radiographic response to RT and OS. Patients were included in the radiographic response analyses if they: (*1*) had measurable brain parenchymal disease before RT; and (*2*) were evaluated by magnetic resonance imaging (MRI) after RT and prior to other CNS-directed therapy. Two experienced neuroradiologists (T.L.C. and T.H.V.) recorded the radiographic responses. For interobserver disagreement, they met to formulate a consensus response assessment. A CR was defined as resolution of gadolinium-enhancing abnormalities; partial response (PR), as $\geq$50% reduction; stable disease (SD), as $<$50% reduction to $<$25% growth; and progressive disease (PD), as $\geq$25% growth or appearance of any new lesion (11, 12). The product of the axial bidirectional diameters (anteroposterior $\times$ transverse) was used for response assessments (12). Measurements were obtained from axial postcontrast T1 images; fluid-attenuated inversion recovery or T2 signal abnormality was excluded from evaluation. All patients were included in survival analyses, and OS was defined as the time from RT initiation to death from any cause.

Secondary endpoints included CNS disease progression and neurotoxicity after RT. CNS disease progression after RT was defined as new or progressive disease involving the cerebrospinal fluid (CSF), brain, spine, or meninges, as documented by pathologic and/or radiologic criteria. Neurotoxicity was defined as documented short-term memory impairment, confusion, gait abnormality, and/or bladder or bowel incontinence that was new or progressive after RT, in the absence of CNS disease progression (13). To be included in toxicity analyses, patients must have had follow-up $>$1 month after RT completion.

Statistics

Survival analyses were performed using Kaplan-Meier methods, with outcomes compared using the log-rank test. To assess OS as a function of disease response, a landmark analysis was used. Multiple publications have stressed that comparing the survival of responders with that of nonresponders by use of typical survival analyses leads to misleading conclusions. This bias results in part from the fact that responders must live long enough for the disease response to be observed, but there is no such requirement for nonresponders. One valid approach to compare OS by response category is the landmark method, which determines each patient's response at a fixed time point. Survival estimates are calculated from that "landmark" time point, and associated statistical tests are conditional on patients' landmark responses (14). As in previously published, similar work, a landmark time of 4 months after RT initiation was used (15), because disease response to RT should have been maximal by this time.

Results

Patient and initial treatment characteristics

Initial DLBCL diagnosis

The cohort comprised 44 patients with systemic DLBCL secondarily involving the brain and/or leptomeninges who received RT as a component of their care. Of these patients, 3 (7%) had CNS involvement at their initial lymphoma

diagnosis, and 41 (93%) experienced a CNS relapse after treatment of systemic DLBCL. Table 1 summarizes the cohort's characteristics at the initial diagnosis with DLBCL. These patients had high-risk disease, characterized by an advanced stage, multiple extranodal sites, high Ki-67 expression, and a high International Prognostic Index score. The most common first-line chemotherapy was R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; n = 34, 77%).

Table 1 Baseline characteristics at initial diagnosis with DLBCL

Characteristic	Data
Age	
>60 y, n	15 (34%)
Median (range), y	55 (23-83)
Male sex, n	30 (68%)
DLBCL subtype, n	
GCB type	9 (21%)
Non-GCB type	8 (18%)
Primary mediastinal	1 (2%)
Unknown	26 (59%)
Stage III-IV	14 (32%)
CNS involvement at initial diagnosis, n	3 (7%)
No. of extranodal sites, n	
0	10 (23%)
1-2	18 (41%)
>2	16 (36%)
Involvement of high-risk extranodal site, n	
Renal or adrenal	8 (18%)
Breast	5 (11%)
Testicle	2 (5%)
Pathologic markers,* n	
Ki-67 expression > 70% (available for n = 29)	24 (83%)
MYC, n	
IHC positive (available for n = 4)	4 (100%)
FISH rearranged (available for n = 11)	2 (18%)
BCL2, n	
IHC positive (available for n = 24)	20 (83%)
FISH positive (available for n = 8)	3 (38%)
BCL6, n	
IHC positive (available for n = 25)	22 (88%)
FISH positive (available for n = 3)	1 (33%)
International Prognostic Index* (available for n = 20), n	
0-1	2 (10%)
2-3	8 (40%)
4-5	10 (50%)
First-line chemotherapy, n	
R-CHOP	34 (77%)
R-hyper-CVAD	5 (11%)
DA-R-EPOCH	3 (7%)
Other	2 (5%)

Abbreviations: CNS = central nervous system; DA-R-EPOCH = dose-adjusted rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin; DLBCL = diffuse large B-cell lymphoma; FISH = fluorescence in situ hybridization; GCB = germinal center B-cell–like; IHC = immunohistochemistry; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-hyper-CVAD = rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

* Data not available for complete cohort.

Diagnosis with CNS involvement

Table 2 summarizes the cohort's characteristics at diagnosis with CNS disease. CNS involvement was identified at a median of 10 months (range, 0-130 months) after the primary lymphoma diagnosis. At this time, 15 patients (34%) had active systemic disease. Patients had received a median of 1 line of chemotherapy (range, 0-5 lines). Before identification of CNS involvement, 14 patients (32%) had received prophylactic CNS-directed chemotherapy, 6 (14%) had undergone autologous SCT, and 3 (7%) had undergone allogeneic SCT. CNS disease involved only the brain parenchyma in 25 patients (57%), only the leptomeninges in 9 (20%), and both in 10 (23%).

Table 2 Characteristics at time of CNS DLBCL detection

	Data
Months from initial diagnosis, median (range)	10 (0-130)
Active systemic disease at time of CNS involvement, n	15 (34%)
Therapy prior to CNS involvement	
Lines of conventional dose chemotherapy, median (range)	1 (0-5)
Prophylactic CNS-directed chemotherapy, n	14 (32%)
Autologous SCT, n	6 (14%)
High-dose chemotherapy	
R-BEAM	4 (67%)
Gemcitabine, busulfan, melphalan, vorinostat	1 (17%)
Busulfan, melphalan	1 (17%)
Allogeneic SCT, n	3 (7%)
Conditioning regimen	
Fludarabine, cyclophosphamide, rituximab	3 (100%)
Donor	
Matched related donor	2 (67%)
Matched unrelated donor	1 (33%)
Lumbar puncture at time of CNS DLBCL detection, n	
Positive for DLBCL	18 (41%)
Negative for DLBCL	11 (25%)
Unknown or not done	15 (34%)
Radiographic findings at time of CNS DLBCL detection, n	
Isolated brain parenchymal disease	25 (57%)
Deep brain involvement*	12 (48%)
Multiple lesions	16 (64%)
Isolated leptomeningeal disease	9 (20%)
Brain parenchymal and leptomeningeal disease	10 (23%)
Deep brain involvement*	8 (80%)
Multiple lesions	6 (60%)
Initial therapy after diagnosis with CNS involvement, n	
Chemotherapy	31 (70%)
Radiation therapy	13 (30%)

Abbreviations: CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; R-BEAM = rituximab, carmustine, etoposide, cytarabine, and melphalan; SCT = stem cell transplantation.

* Periventricular regions, basal ganglia, brainstem, and/or cerebellum.

Initial management of CNS disease

Chemotherapy was the initial treatment given after the identification of CNS involvement in 31 patients (70%). In 30 of these (97%), the regimen included MTX. A median of 1 line of chemotherapy (range, 1-4 lines) was given after the diagnosis of CNS DLBCL and prior to RT. Among evaluable patients (n = 30), the best response to CNS-directed chemotherapy achieved was a CR in 4 (13%), PR in 6 (20%), and SD or PD in 20 (66%). Of the 4 patients with a CR, 2 received RT with consolidative intent and 2 experienced intracranial disease progression prior to salvage RT.

RT information

Table 3 summarizes the cohort's characteristics at the time of RT initiation. Thirty-four patients (77%) had neurologic symptoms, and 42 (95%) had radiographic evidence of disease. At the initiation of RT, 14 patients (32%) had active extracranial disease.

RT consisted of whole-brain RT (WBRT) in 42 patients (95%). Of these, 13 (31%) received a boost to the gross disease. The median WBRT dose for patients not treated with a boost was 30 Gy (range, 18-30.6 Gy). For patients who received a boost, the median WBRT dose was 27 Gy (range, 20-32.5 Gy), the median boost dose was 9 Gy (range, 5-20 Gy), and the median total dose (WBRT plus boost) was 39 Gy (range, 30.6-45 Gy). One patient received partial-brain RT because his disease had relapsed 3 times in the same isolated brain parenchymal site, and he had received orbital RT previously that precluded receiving WBRT without exceeding normal tissue tolerance; the dose was 44 Gy. The remaining patient was treated with craniospinal irradiation (CSI) to 30 Gy. In all cases, RT was administered in daily fractions with a median dose of 2 Gy (range, 1.8-3 Gy).

Table 3 Characteristics at initiation of RT

	Data
Age > 60 y, n	21 (48%)
Salvage CNS-directed chemotherapy given prior to RT, n	31 (70%)
CNS-directed chemotherapy included MTX, n	30 (97%)
Lines of salvage chemotherapy, median (range)	1 (1-4)
Allogeneic stem cell transplantation, n	1 (3%)
Best response to CNS-directed chemotherapy (n = 30 evaluable patients), n	
Complete	4 (13%)
Partial	6 (20%)
None	20 (66%)
Neurologic symptoms at initiation of RT,* n	34 (77%)
Peripheral motor and/or sensory symptoms	16
Cranial neuropathy	14
Headache	12
Altered mental status	11
Altered gait and/or balance	9
Seizure	6
Radiographic evidence of disease at initiation of RT, n	42 (95%)
Active extracranial disease at time of RT, n	14 (32%)

Abbreviations: CNS = central nervous system; MTX = methotrexate; RT = radiation therapy.
* More than 1 neurologic symptom per patient was possible.

Radiographic and clinical response to RT

A total of 26 patients (59%) were eligible for radiographic response assessments. The remaining 18 patients were not included because either measurable disease was not present prior to RT or MRI was not performed after RT. Response assessments were based on MRI scans performed a median of 5 weeks (range, 1-23 weeks) after completion of RT. In 22 cases (85%), MRI scans were performed between 2 and 10 weeks after the completion of RT. The response was a CR in 11 patients (42%), PR in 12 (46%), and SD in 3 (12%). There was no instance of PD. The overall response rate (CR plus PR) was 88%.

At the time of RT initiation, 34 patients (77%) had neurologic symptoms. These included peripheral motor and/or sensory deficits (36%), cranial neuropathy (32%), headache (27%), mental status changes (25%), altered gait and/or balance (20%), and seizure (14%) (>1 symptom per patient was possible). Of these patients, 26 (76%) experienced a documented improvement in their neurologic symptoms during or within 1 month after completion of RT. In addition to RT, patients were treated with steroids (n = 32) and antiseizure medication (n = 6).

SCT after RT

SCT was performed after RT in 8 patients (18%). Of these, 6 received CNS-directed induction chemotherapy after CNS disease identification and before RT, which resulted in a CR in 1, PR in 3, and SD or PD in 2. For the 7 patients with radiographic evidence of disease at RT initiation, the response to RT was a CR in 4 and PR in 3.

Following RT, 7 patients were treated with autologous SCT and 1 with allogeneic SCT. The high-dose chemotherapy used with autologous SCT was R-BEAM (rituximab, carmustine, etoposide, cytarabine, and melphalan) in 4 patients, and carmustine and thiotepa in 3. The conditioning regimen used with allogeneic SCT was R-BEAM, and the donor was an HLA-identical sibling.

Survival after RT

At a median of 31 months after RT, 18 instances of disease progression outside the CNS and 30 deaths were observed. Median OS was 7 months (95% confidence interval [CI] 4-10 months), the 1-year OS rate was 38% (95% CI 23%-53%), and the 2-year OS rate was 31% (95% CI 16%-46%). Subsequently, the OS curve plateaued, with the 31% OS rate extending from 2 to 8 years (Fig. 1A).

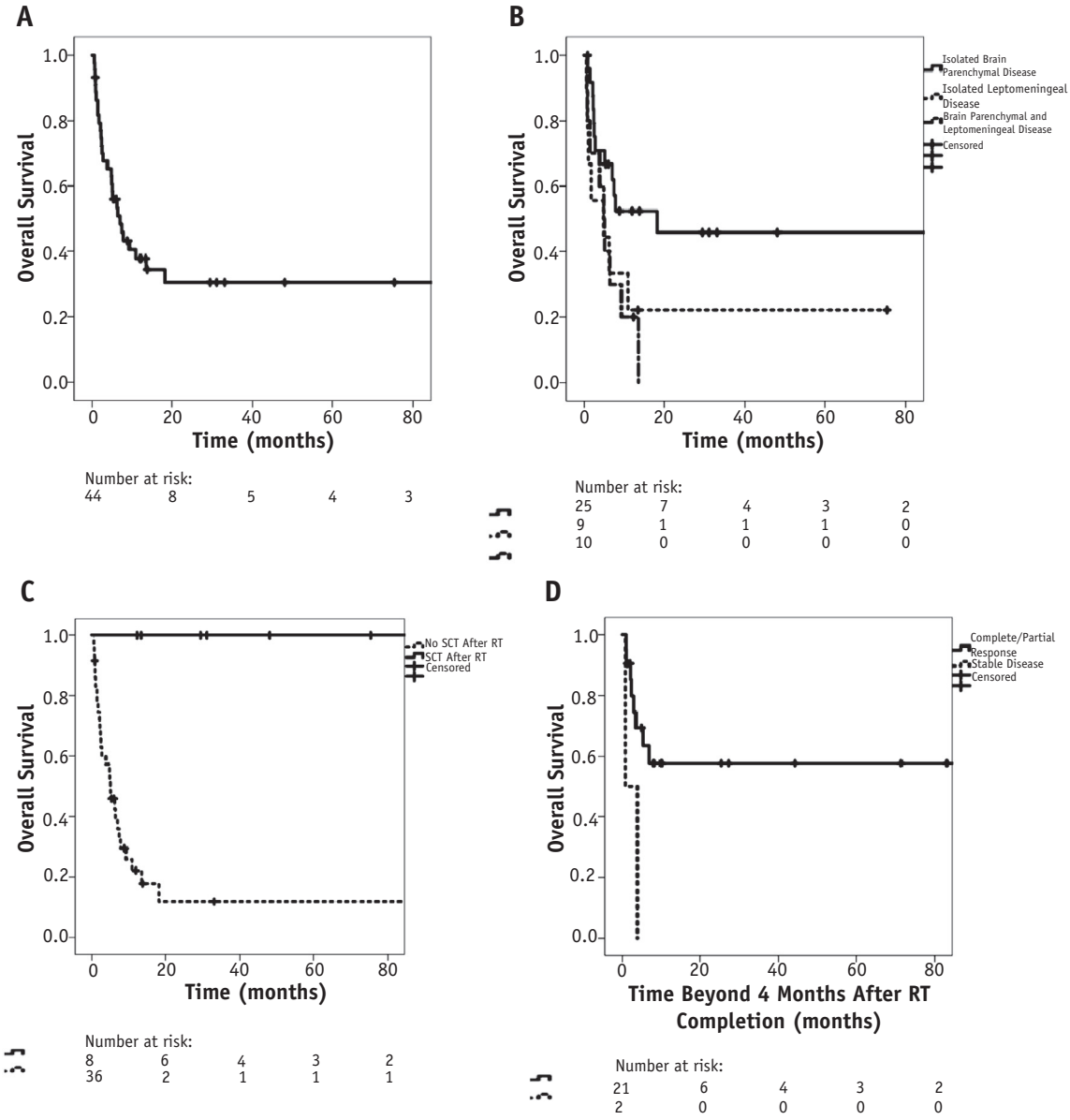

Fig. 1. Kaplan-Meier curves for overall survival from start of radiation therapy (RT). A, Overall survival for complete cohort. B, Overall survival according to localization of central nervous system disease (isolated brain parenchymal disease, n = 25; isolated leptomeningeal disease, n = 9; brain parenchymal and leptomeningeal disease, n = 10), with $P = .05$. C, Overall survival according to stem cell transplantation (SCT) after RT (SCT, n = 8; no SCT, n = 36), with $P < .001$. D, Overall survival beyond the landmark time according to radiographic response status (complete or partial response, n = 21; stable disease, n = 2), with $P = .03$.

We assessed for an association of covariates with OS (Table 4). Patients with isolated brain parenchymal disease experienced superior OS after RT compared with those with leptomeningeal disease (LMD) ($P = .05$, Fig. 1B). In addition, among patients who received CNS-directed induction chemotherapy before RT, those with a CR or PR experienced better survival ($P = .08$).

The factor with the greatest influence on OS was SCT after RT ($P < .001$; Table 4, Fig. 1C). At a median follow-up of 31 months for patients treated with SCT after RT (n = 8), the 3-year OS rate was 100%. One death was observed at 103 months after RT. This patient died of unknown cause and was without evidence of disease at last follow-up. Patients selected for SCT were significantly younger ($P = .02$); in addition, they must have been fit and had disease that was responsive to therapy to be considered candidates for SCT.

In patients who did not undergo SCT after RT (n = 36), median OS was 5 months (95% CI 2-8 months). In this subgroup, 5 patients (14%) survived >1 year after RT. The longest survival time was 95 months after RT, at which time this patient was disease-free.

Table 4 Univariate analyses of factors associated with overall survival after RT

	n	OS, median (95% CI), mo	Log-rank *P* value
Total cohort	44	7 (4-10)	
Age at initial DLBCL diagnosis			
<60 y	29	7 (2-12)	.8
>60 y	15	6 (2-10)	
Age at time of RT			
<60 y	23	9 (0-20)	.4
>60 y	21	6 (4-9)	
Active systemic disease at time of CNS DLBCL detection			
Yes	15	6 (0-13)	.4
No	29	7 (3-11)	
Active systemic disease at time of RT			
Yes	14	5 (2-8)	.3
No	30	8 (1-14)	
Site of CNS involvement			
Isolated brain parenchymal disease	25	18 (0-74)	
Isolated leptomeningeal disease	9	5 (0-14)	.05*
Brain parenchymal and leptomeningeal disease	10	5 (3-7)	
Salvage CNS-directed chemotherapy given prior to RT			
Yes	31	6 (3-10)	.5
No	13	7 (4-11)	
Best response to salvage CNS-directed chemotherapy given prior to RT (n = 30)			
Response (CR or PR)	10	14†	.08
No response (SD or PD)	20	4 (0-9)	
Stem cell transplantation after RT			
Yes	8	3-y OS, 100%‡	<.001*
No	36	5 (2-8)	
Radiographic response to RT§			
CR or PR	21	7-mo OS, 58%‡	.03*
SD	2	0.8†	

Abbreviations: CI = confidence interval; CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; OS = overall survival; PD = progressive disease; PR = partial response; RT = radiation therapy; SD = stable disease.

* Statistically significant.

† Insufficient number of events after median OS time to calculate 95% CI.

‡ Did not reach median OS.

§ Survival beyond landmark time of 4 months. Only patients eligible for radiographic response assessment who were alive at 4 months after RT were included.

We evaluated the association between radiographic response to RT and OS using a landmark analysis. To be included, patients must have been: (*1*) eligible for radiographic response assessments; and (*2*) alive at the landmark time. Among the 23 patients who met these criteria, the response status was a CR or PR in 21 (91%) and SD in 2 (9%). Median OS beyond the landmark time was not reached in the CR-PR subgroup and was 0.8 months in the SD subgroup (P = .03; Table 4, Fig. 1D).

CNS disease progression after RT

CNS disease progression was observed after RT in 8 patients (18%). All 8 CNS relapses occurred after RT to the brain alone; the sole patient treated with CSI had durable CNS disease control at 14 months after RT.

In 1 case, progression occurred in the brain parenchyma within the boost volume that had received 36 Gy. This relapse occurred 4 months after RT in a patient who had achieved an initial PR to RT. The other 7 CNS relapses involved the spine and/or CSF and/or meninges. In 5 of these 7, there was no radiographic evidence of intracranial progression, consistent with relapse entirely outside the RT field; in the remaining 2, enhancement of the cranial nerves or ventricles was observed, in combination with CSF positivity, suggesting progression both within and outside the RT field. The spinal/CSF/meningeal relapses were diagnosed at a median of 7 months (range, 2-14 months) after RT. Among the 7 patients with disease relapse after RT that involved the spine, CSF, and/or meninges, CSF studies from the time of initial identification of CNS disease were available for 5 and showed positive results for lymphomatous involvement in 3. Of these 7 patients, 4 experienced progression outside the CNS as well: in 1 patient, disease progressed outside the CNS 7 months before its detection in the spine; in the other 3, CNS disease relapse and extra-CNS disease relapse were identified concurrently. In the 3

remaining cases, the patients died with progressive CNS disease, without evidence of systemic recurrence.

We assessed for factors associated with CNS disease progression after RT. CNS relapse was observed in 3 of 25 patients (12%) with isolated brain parenchymal disease and 5 of 19 patients (26%) with LMD with or without brain parenchymal disease ($P = .2$). CNS relapse was not associated with radiographic response to RT ($P > .99$) or with other treatment-related factors, including receipt of CNS-directed chemotherapy prior to RT ($P = .7$) or SCT after RT ($P = .6$). We could not assess the association of CSI with CNS disease control because only 1 patient was treated with this approach.

Toxicity after RT

Patient charts were searched for documentation of possible neurotoxicity after RT (13). Eligible patients: (*1*) had follow-up >1 month after RT; and (*2*) did not experience CNS disease progression. Of the 27 patients who met these criteria, 7 (26%) had documented new or progressive deficits after RT. Of these, 3 (43%) had similar deficits prior to RT with worsening after RT. At the time of RT, 3 (43%) were aged ≥60 years. SCT was performed before or after RT in 5 (71%). No case of grade 5 neurotoxicity was observed. No association of neurotoxicity with RT dose or fraction size was observed.

Special attention was focused on neurotoxicity in patients who underwent SCT after RT, because they experienced prolonged survival, so late adverse effects are of particular importance. Of the 8 patients in this subgroup, 3 reported a decline in memory after treatment. In 2, who were aged 31 and 52 years at the time of RT, the memory deficit was mild: they were working full-time and were assigned a Karnofsky Performance Status of 100% at their last follow-up. The third patient, who was aged 64 years at the time of RT and SCT, experienced more significant memory deterioration, as well as urinary incontinence. She reported both symptoms prior to RT, with progression after RT. Of note, she had comorbid neuropsychological conditions: she experienced a cerebrovascular accident soon after the SCT, with a subsequent seizure disorder and major depressive disorder.

Discussion

RT is an effective treatment strategy for DLBCL secondarily involving the brain and/or leptomeninges. In this cohort, we identified a radiographic response (CR or PR) in 88% of cases and clinical improvement in 76% of patients who had neurologic symptoms at RT initiation. These outcomes were observed even though most patients were heavily pretreated and had experienced a poor CNS disease response to chemotherapy. Our findings suggest that SCNSL remains responsive to RT even if it has been refractory to other CNS-directed therapy. Furthermore, long-term disease-free survival was observed in a subset of patients. Although most patients died within 2 years, reflecting the poor prognosis of this condition, the survival curve plateaued subsequently, with a 31% OS rate extending from 2 to 8 years after RT. OS was particularly favorable for patients who underwent subsequent SCT; however, long-term disease-free survival was observed in some individuals after salvage RT even in the absence of SCT.

These results corroborate previously reported findings. In a series of 36 patients treated with RT for primary CNS lymphoma or SCNSL that was refractory to or relapsed after MTX, the overall response rate was 67% (50% CR, 17% PR), and 22% of patients were alive and disease-free >3 years after salvage RT (10). The median OS was 8.6 months for the subset with SCNSL. This previously reported cohort included patients with marginal zone and mantle cell lymphoma, in addition to DLBCL, and included patients with isolated orbital or spinal involvement, in addition to intracranial disease. In our study, we limited our analysis to patients with DLBCL secondarily involving the brain and/or leptomeninges. Thus, our study confirmed previously reported radiographic response rates and survival outcomes in a more homogeneous cohort.

The efficacy of RT for the palliation of neurologic symptoms from SCNSL was an important finding of this study. To our knowledge, little has been published on this topic previously. One other group did report that 6 of the 9 patients (67%) in their cohort who were treated with RT for SCNSL experienced an improvement in neurologic symptoms (3), consistent with our findings. In our cohort, it was difficult to accurately ascertain the duration of palliation, given the lack of standardized follow-up; therefore, future prospective study is encouraged.

The dominant pattern of relapse observed after RT was with distant systemic disease. Specifically, progression after RT involved the CNS in 8 cases and sites outside the CNS in 18. The opposite pattern has been observed in cohorts treated with high-dose chemotherapy and SCT without RT. For example, in a series published by Ferreri et al (8), patients were treated with MTX, high-dose immunochemotherapy, and SCT. Subsequent disease progression involved the CNS in 13 of 17 cases. These patterns suggest complementary roles of RT and high-dose chemotherapy/SCT to maximize local and distant disease control, respectively. A critical consideration is the risk of neurotoxicity in patients treated with both RT and high-dose CNS-penetrating chemotherapy (16, 17), arguing against the routine use of combination therapy in all patients. However, appropriately selected patients with refractory disease may benefit from treatment with both RT and high-dose chemotherapy/SCT. In our cohort, most patients treated with RT prior to SCT had persistent or progressive CNS disease after induction chemotherapy, which responded favorably to RT. Subsequently, they underwent SCT and experienced excellent survival outcomes. These findings suggest that RT may provide CNS disease control that

facilitates successful salvage with SCT in selected patients with chemotherapy-refractory disease.

Local control within the RT field was good, with only 1 brain parenchymal disease relapse observed in a patient who achieved an initial PR. However, 7 patients experienced disease relapse involving the spine and/or CSF and/or meninges. Of these, 3 died with progressive CNS lymphoma, without evidence of systemic relapse, highlighting the importance of establishing CNS disease control. All 7 patients with CNS disease progression had received cranial RT; conversely, the sole patient treated with CSI had durable CNS disease control at 14 months of follow-up. These findings suggest a possible role for comprehensive irradiation of the craniospinal axis in appropriately selected patients. To determine which patients may benefit from CSI, we assessed for factors associated with CNS relapse. No covariate was significantly associated with CNS disease progression after RT, likely because of the small number of events. Although it did not reach statistical significance, patients with LMD were at higher risk of CNS disease progression than those with isolated brain parenchymal disease. Therefore, it may be hypothesized that select patients with LMD may benefit from CSI. CSI may be advantageous in these patients because comprehensive treatment of the neuraxis may be necessary to sterilize the circulating CSF. Further study is needed to explore the role of CSI in this setting.

This work has several limitations. We attempted to create a homogeneous cohort by including only patients with DLBCL secondarily involving the brain and/or leptomeninges. Nonetheless, significant variability existed in baseline characteristics and treatment strategies, in part reflecting the lack of consensus regarding the optimal management of these patients. In addition, the time to response evaluation varied widely, with MRI scans performed anywhere from 1 to 23 weeks after RT completion; most scans (85%) were performed between 2 and 10 weeks after RT. The loose time frame in which response assessments were performed may have influenced our findings. It is also possible that patients with poor disease response did not survive long enough for reassessment by MRI. Furthermore, the small patient numbers limited statistical testing, particularly for subgroup or multivariable analyses. Therefore, we cannot exclude the possibility that confounders affected our findings. For example, the patients who underwent SCT or had disease that responded radiographically to RT may have experienced superior OS because of the presence of other favorable prognostic factors. For example, young, fit patients with chemoresponsive disease are selected preferentially for SCT (18), which likely contributes to their improved survival outcomes. Last, neurotoxicity assessments were limited, because standardized neurocognitive evaluations were not performed as a part of this retrospective study. No grade 5 neurotoxicity was observed; however, further classification of adverse events was not possible. Furthermore, because the cohort was small and managed heterogeneously, it was not possible to assess for differences in the risk of neurotoxicity according to treatment approach or sequencing; for example, we could not reliably compare the risk of neurotoxicity in patients treated with RT before versus after SCT.

Despite these limitations, to our knowledge, this study represents the largest report of SCNSL patients treated with RT. Our findings suggest that RT provides high response rates and can contribute to long-term disease-free survival. Future prospective studies with uniform treatment, standardized follow-up, and formal neurocognitive evaluations are encouraged to further define the role of RT in this setting.

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