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Scientific Article

Response-adapted radiation therapy for newly diagnosed primary diffuse large B-cell lymphoma of the CNS treated with methotrexate-based systemic therapy

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Abstract

Background: For patients with primary diffuse large B-cell lymphoma of the central nervous system (PCNSL), whole-brain radiation therapy (WBRT) to doses of $\geq$45 Gy are often given after a partial response (PR) to methotrexate-based induction chemotherapy. We conducted an

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exploratory analysis to determine whether lower-dose WBRT, given with a boost to sites of persistent disease, might be a reasonable alternative.

Methods and materials: We retrospectively reviewed the records of 22 patients with PCNSL who received WBRT, with or without a boost, after methotrexate-based induction chemotherapy. Outcomes were compared among patients according to response to chemotherapy using the Kaplan-Meier method.

Results: Median follow-up was 52 months. All patients with a complete response (CR) (n = 5) received WBRT to 23.4 Gy. One CR patient died after an in-field relapse. Patients with partial response (PR) (n = 10) received a median whole-brain dose of 23.4 Gy with (n = 8) or without (n = 2) a boost; there were 2 relapses within the central nervous system (CNS). All PR patients were alive at the time of analysis. The overall survival (P = .127) and freedom from relapse within the CNS (P = .967) were not different for patients with CR versus PR. Baseline and follow-up neurocognitive evaluations were available for 4 PR patients, and there were no significant differences between pre- and post-treatment evaluations (P > .05 for language, memory, visual-spatial, attention, or motor functions). All patients who progressed or did not respond to chemotherapy and then received WBRT had died at a median time of 3.4 months. Patients who progressed or did not respond to chemotherapy had worse overall survival (P = .001) and freedom from CNS relapse (P = .005) compared with CR patients.

Conclusions: Among patients with a PR to induction chemotherapy, reduced-dose WBRT with a boost to residual PCNSL may be a viable treatment approach that merits further investigation.

Introduction

The role of radiation therapy (RT) in the management of primary diffuse large B-cell lymphoma of the central nervous system (PCNSL) remains controversial. Historically, definitive radiation doses of 50 to 60 Gy led to inadequate disease control, with most patients developing recurrent central nervous system (CNS) disease within the radiation field.[1,2] The advent of high-dose methotrexate-based polychemotherapy[3] has resulted in adjustments in radiation-based treatment strategies, mainly because of the high rates of neurotoxicity after combined-modality therapy, especially among patients ages >60 years.[4] Retrospective studies have identified a complete response (CR) to induction chemotherapy as a strongly favorable prognostic factor, suggesting that subgroups of patients may benefit from treatment deintensification.[5] As a result, various treatment approaches have emerged for patients who achieve a CR to induction chemotherapy, including dose-reduced whole-brain RT (WBRT)[6-8] or deferring radiation in favor of consolidative chemotherapy[9-11] or stem cell transplant.[12,13]

Up to a quarter of patients will achieve a partial response (PR), even after several cycles of methotrexate-based induction polychemotherapy (MIC), which typically consists of high-dose methotrexate, procarbazine, vincristine, and cytarabine with or without rituximab.[8,14-16] Currently, patients with a PR to MIC for whom RT is considered often receive doses of 45 Gy to the whole brain.[17,18] The efficacy of reduced-dose WBRT, which may reduce neurotoxicity[19] and is accepted in the setting of a CR, is not well defined for patients with a PR to MIC. Accordingly, we performed an exploratory analysis of patients with PCNSL who had been treated with radiation at our institution, hypothesizing that patients with a PR to MIC who were then treated with reduced-dose WBRT coupled with dose-escalation or a boost limited to areas of persistent disease could achieve favorable outcomes.

Methods and materials

The medical records of patients who presented to our department for management of PCNSL between 2007 and 2016 were reviewed. Patients who received consolidative radiation after achieving a CR or PR to MIC were selected for inclusion. Patients with stable disease (SD) or progressive disease (PD) in response to MIC who underwent WBRT were included. Patients with relapsed disease were only included if WBRT was a component of first-line salvage therapy. Patients who received upfront autologous stem cell transplant (ASCT) before evidence of relapse or progressive disease were excluded. Patients who did not undergo WBRT and patients with secondary diffuse large B-cell lymphoma involving the CNS (ie, diagnosis of lymphoma initially at a non-CNS site) were excluded. The institutional review board approved this retrospective study.

First-line induction chemotherapy consisted of high-dose intravenous methotrexate-based regimens (range, 2.5-8.0 g/m^2). Patients were treated with combinations of methotrexate, procarbazine, vincristine, cytarabine, rituximab, and temozolomide. WBRT was administered at

least 2 weeks after the last cycle of methotrexate. Before WBRT was initiated, all patients underwent a treatment-planning computed tomography (CT) scan in the radiation-treatment position, with a thermoplastic mask for immobilization. The WBRT dose was prescribed to the midcranial isocenter and was delivered by using laterally opposed fields.

For patients with concurrent ocular disease, the entire globes were included in the radiation field; otherwise, the posterior half of the globe was included for patients without known ocular involvement. Boost doses were delivered sequentially by using intensity modulated RT, volumetric modulated arc RT, or 3-dimensional conformal techniques to sites of persistent disease, as identified on contrast-enhancing magnetic resonance imaging (MRI) scans. Areas of surrounding T2 or fluid-attenuated inversion recovery abnormality were included in the boost field at the discretion of the treating radiation oncologist.

Patients underwent contrast-enhanced MRI of the brain as a component of the diagnostic workup and for follow-up. Responses were assessed based on an MRI scan obtained after completion of all systemic therapy but before WBRT. Responses were categorized in accordance with the PCNSL Collaborative Group Criteria as CR or unconfirmed complete response (CRu), PR, or PD.[20] A neuroradiologist interpreted the MRI scans and grouped patients accordingly; a second neuroradiologist provided review and confirmation as needed.

Neurocognitive evaluations were performed at the discretion of the treating physician by a neuropsychiatrist and a psychometrist. Five domains (attention, language, memory, visuospatial, and motor function) were assessed using the Weschsler Adult Intelligence Scale, Hopkins Verbal Learning Test, Boston Naming Test, Controlled Oral Word Association, Token Test, Line Bisection Test, Trail Making Test, Grip Strength, and Grooved Pegboard Test. The summarized results across the 5 domains were transformed into an ordinal scale: superior (3), high average (2), low average (1), average (0), mild impairment (−1), moderate impairment (−2), or severe impairment (−3). Within each domain, the Wilcoxon matched-pairs signed-rank test was used to assess differences between scores before and after treatment.

The Kaplan-Meier method was used to compare outcomes between response groups. t_0 was defined as the start date of radiation. Dates of death were confirmed through medical records, Social Security death records, or published newspaper obituaries. The follow-up time was defined as the interval between t_0 and the last follow-up date of living patients. For overall survival (OS), living patients were censored at last follow-up. For freedom from CNS relapse (FFCR), an event was defined as disease progression within the brain parenchyma. Patients without progression were censored on the date of the last MRI brain study or at the time of death if no MRI brain studies had been obtained. For progression-free survival, an event was defined as lymphoma progression at any site or death from any cause. The log-rank test was used to test the equivalence between different subgroups. Corrections were not made for multiple comparisons given the exploratory nature of the study. Statistical analyses were done with Stata software (College Station, TX).

Results

Patients and treatment

A total of 68 patients who presented to the radiation oncology department with a diagnosis of primary B cell lymphoma of the CNS were identified. Forty-four patients (66%) were excluded because they did not receive radiation. The reasons for omission of radiation were declining radiation or disposition to observation after a CR to induction (n = 25; 35%), consolidation with ASCT (n = 11; 15%), treatment with salvage chemotherapy for progression/relapse, and death before completion of chemotherapy (n = 8; 11%). Two patients who received additional ASCT in the upfront setting were also excluded.

Twenty-two patients (32%) satisfied the inclusion criteria. Patient and treatment data are summarized in Table 1. Half of the patients were female, and a slight majority (52%) presented with a favorable performance status (Eastern Cooperative Oncology Group score of 0-1). After a median of 5 cycles of MIC, 5 patients had a CR, 10 had a PR, and 7 had SD/PD. Five of 7 patients in the SD/PD subgroup had PD throughout the MIC, and the 2 others had PD after completion of systemic therapy and were treated with upfront salvage radiation. Two of 20 patients tested positive for HIV, and both patients were in the CR subgroup.

The median whole-brain dose for all patients was 26.7 Gy (range, 23.4-45.0 Gy), and the median total dose including the boost was 33.75 Gy (range, 23.4-45.0 Gy). CR patients received reduced-dose WBRT (23.4 Gy in 1.8 Gy, once-daily fractions). For the PR patients, the median WBRT dose was 23.4 Gy (range, 23.4-36.0 Gy) with fraction sizes ranging from 1.8 to 2.0 Gy/day. Six PR patients received reduced-dose WBRT, and 8 patients received a sequential radiation boost dose to residual areas of radiographic abnormality in 1.8 Gy, once-daily fractions to a median total dose of 37.8 Gy (range, 30.0-45.0 Gy). Two patients ultimately underwent ASCT with rituximab, melphalan, etoposide, cytarabine, and carmustine as salvage therapy for relapsed disease after completion of MIC and WBRT. PD or SD patients received WBRT to a median dose of 30.6 Gy (range, 30.0-45.0 Gy) in 1.8 Gy to 3.0 Gy daily fractions, administered either with (n = 2) or without (n = 5) a boost to sites of active lymphoma. The median total dose for the PD/SD patients was 33.3 Gy. Boost doses were

Table 1 Patient and treatment characteristics

Characteristics	All patients (n = 22)	Complete response (n = 5)	Partial response (n = 10)	Progressive or stable disease (n = 7)
Patients				
Male sex, n (%)	11 (50)	0	6 (60)	5 (71)
Median age, years [range]	60 [31-77]	54 [31-71]	57.5 [39-68]	66 [36-77]
Deep brain involvement, n (%)	13 (59)	1 (20)	8 (80)	4 (57)
ECOG performance score, n (%)				
0-1	17 (52)	5 (100)	8 (80)	4 (57)
2-3	4 (18)	0	1 (10)	3 (43)
Mean initial LDH level, [range]	598 [152-1288]	766 [358-1288]	574 (152-1091)	473 [199-715]
Radiation				
No. given radiation boost (%)	10 (45)	0	8 (80)	2 (29)
Median whole-brain dose, Gy [range]	26.7 [23.4-45.0]	23.4 [23.4-23.4]	23.4 [23.4-36.0]	30.6 [30.0-45.0]
Median boost dose, Gy [range]	12.6 [5.5-21.6]	Not applicable	13.5 [7.2-21.6]	7.5 [5.5-14.4]
Median total dose, Gy [range]	33.75 [23.4-45.0]	23.4 [23.4-23.4]	37.8 [30.0-45.0]	33.3 [30.0-45.0]
Chemotherapy				
Median no. cycles methotrexate-based induction chemotherapy [range]	5 [1-9]	5 [4-7]	5.5 [1-9]	4 [2-5]
Median dose of methotrexate, g/m^2	3.5 [2.5-8.0]	3.5 [3.5-3.5]	3.5 [3.0-8.0]	3.5 [2.5-6.0]
High-dose Ara-C given	15 (68)	5 (100)	5 (50)	5 (71)
Intrathecal chemotherapy	4 (18)	0	1 (10)	3 (43)
Given rituximab before radiation, n (%)	17 (77)	5 (100)	7 (70)	5 (71)
Survival				
Median follow-up time of survivors [range]	51.9 [0.7-125.9]	46.7 [20.5-77.9]	51.9 [0.7-125.9]	Not applicable
Median OS time (95% CI)	52.3 (55-N/A)	Not reached	Not reached	3.4 (1.2-14.2)
Median FFCR time (95% CI)	66.6 (36.6-N/A)	Not reached	66.6 (66.6-N/A)	11.6 (1.7-N/A)
Median PFS time (95% C.I.)	52.3 (5.5-N/A)	Not reached	66.6 (12.0-N/A)	3.0 (0.7-5.5)
Log rank test for OS (vs. CR)			0.1266	0.0012
Log rank test for FFCR (vs. CR)			0.5770	0.0048
Log rank test for PFS (vs. CR)			0.8583	0.0011

CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group, FFCR, For freedom from central nervous system relapse; LDH, lactate dehydrogenase; N/A, not available; OS, overall survival; PFS, progression-free survival.

delivered sequentially with intensity modulated RT (n = 5), volumetric modulated arc RT (n = 4), or 3-dimensional conformal techniques (n = 1).

Survival analyses

At the time of analysis, 14 of 22 patients were alive. The median follow-up time among survivors was 51.9 months (range, 0.7-125.9 months). For all patients, the median OS time was 52.3 (95% confidence interval [CI], 55.0 to not available [N/A]), median FFCR time was 66.6 (95% CI, 36.6 to N/A), and median progression-free survival was 52.3 (95% CI, 5.5 to N/A) months. The results stratified by response to MIC are shown in Table 1. At the time of analysis, 1 patient in the CR/CRu group had died, all 10 patients in the PR group were alive, and all 7 patients in the SD/PD group had died. The median follow-up time for survivors in the CR group was 46.7 months, with 1 patient dying at 38.7 months. For the PR group, the median follow-up time was 51.9 months. The median OS time for the SD/PD group was 3.4 months.

Curves depicting OS and FFCR over time for all patients are shown in Fig 1. The OS rates were no different between patients with a CR versus a PR to MIC (log-rank P = .1266; Fig 2); however, the difference in OS between the CR/CRu and SD/PD groups was significant (log-rank P = .0012). Similarly, FFCR rates were no different between the CR/CRu and PR groups (Fig 3; log-rank P = .9671); however, the FFCR rates were different for the CR and SD/PD groups (Fig 3; log-rank P = .0011).

Patterns of failure

In the CR/CRu cohort, 2 patients relapsed. MIC for both patients consisted of methotrexate, procarbazine, vincristine, cytarabine, and rituximab. One patient experienced a relapse in the brain at the original site of disease after 5 cycles of MIC and reduced-dose WBRT (23.4 Gy). That patient subsequently received several regimens of systemic therapy, including rituximab, high-dose methotrexate, and temozolomide, but died at 38.7 months after

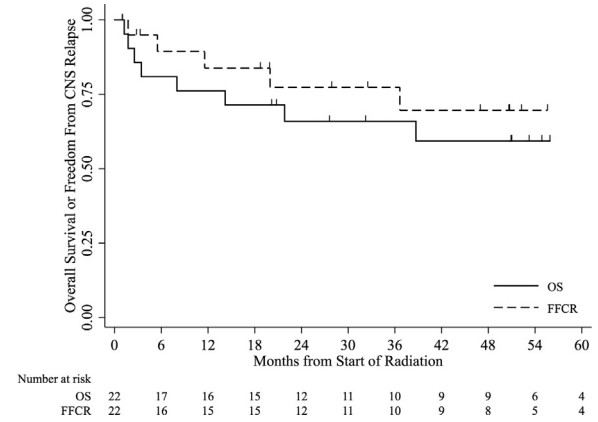

Figure 1 Overall survival and freedom from central nervous system relapse or progression.

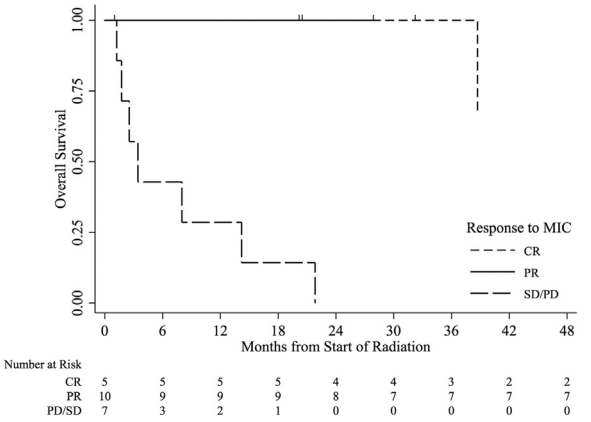

Figure 2 Overall survival stratified by response to methotrexate-based induction chemotherapy. CR, complete response; PR, partial response; SD/PD, stable disease or progressive disease.

starting WBRT. A second patient in the CR/CRu cohort had biopsy-proven progression in the floor of the mouth 16.6 months after completing 7 cycles of MIC and consolidative reduced-dose WBRT (23.4 Gy). This patient was alive after 3 cycles of rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin followed by consolidative radiation to the floor of the mouth to a dose of 30.6 Gy.

Three patients who initially had PR after MIC had recurrent disease after radiation. Two patients who had received 5 cycles of MIC (methotrexate, procarbazine and vincristine, cytarabine, and rituximab) relapsed in the CNS at 52 and 66.6 months after reduced-dose WBRT (23.4 Gy) with a 12.6 Gy boost to residual disease and WBRT to 36.0 Gy, respectively. The former patient relapsed outside of the boost site, was treated with an additional 4 cycles of rituximab, methotrexate, procarbazine, and vincristine, and achieved a CR. The latter patient who relapsed at the site of the original disease was successfully treated with salvage chemotherapy and ASCT and was alive and in complete remission at 37.2 months after ASCT. The third patient who relapsed progressed outside the radiation treatment field in the neck after 6 cycles of MIC (methotrexate, procarbazine, and vincristine) followed by WBRT to 23.4 Gy with an additional 21.6-Gy boost to the residual tumor (total 45.0 Gy). After extraneuroaxial progression was diagnosed at 12 months, further work-up revealed disseminated disease with bone marrow infiltration, for which the patient received salvage chemotherapy and ASCT. This patient was alive at 26.5 months after ASCT.

Disease progression in the CNS was documented in 3 of 7 patients with SD/PD. One patient had progression in the vitreous after full-dose WBRT to 45 Gy and then eventually developed parenchymal brain relapse. The 2 other patients (who had both received a boost dose of radiation) had progression at the original site of disease. The remaining 4 patients died within 4 months of WBRT before a follow-up MRI brain scan could be obtained. One patient was believed to have PD in the cervical nerve roots, 2 other patients received 30 Gy and 33.3 Gy and died within 2.5 months of WBRT, and the remaining patient died 3 months after salvage WBRT (30 Gy in 10 fractions) for disease relapse after initially attaining a CR to MIC. An autopsy of the latter patient showed no evidence of relapse or progression.

Neurotoxicity

Four patients who received reduced-dose WBRT (23.4 Gy) to the whole brain had neurocognitive evaluations before and after WBRT. The median age of these patients was 61 years (range, 52-68 years). All 4 patients had a PR to MIC and received a radiation boost, for a total dose of 34.2 to 45.0 Gy. The median interval between completion of WBRT and neurocognitive assessment was 8.8 months (range, 0.9-23.3 months). Wilcoxon

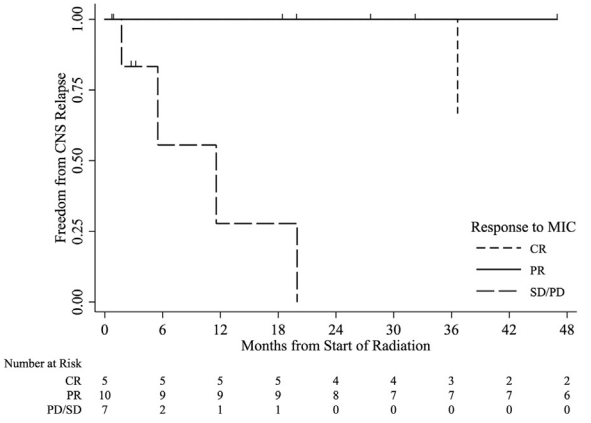

Figure 3 Freedom from central nervous system relapse or failure stratified by response to methotrexate-based induction chemotherapy. CR, complete response; PR, partial response; SD/PD, stable disease or progressive disease.

matched-pairs signed-rank tests showed no significant differences in composite neurocognitive scores across the 5 dimensions: attention ($P = 0.5637$), language ($P = 0.1615$), memory ($P = 0.3173$), visuospatial processing ($P = 0.3173$), and motor coordination ($P = 0.3173$).

One patient experienced biopsy-proven necrosis in this series. This patient had a CR after 7 cycles of rituximab, methotrexate, procarbazine, and vincristine followed by reduced-dose WBRT to 23.4 Gy. At 5.6 months after WBRT, the patient developed paresthesia and expressive aphasia, with MRI scan showing an enhancing area of nodularity near the initial site of CNS lymphoma. The results of 3 subsequent biopsies showed no evidence of disease recurrence. Several courses of bevacizumab therapy, as well as hyperbaric oxygen therapy, were given with partial improvement. Five years after completion of WBRT, this patient was still under surveillance and living independently.

Discussion

Although a significant portion of patients will achieve a PR to methotrexate-based induction chemotherapy, studies have either provided limited information on PR patients or have relegated them to the same treatments as patients who have progressive or relapsed disease.[3,8,10,21,22] Treating with higher doses of radiation (ie, 45 Gy) is not without potential significant toxicity. Grade 5 treatment-related neurotoxicity has been reported to be as high as 25% among patients treated to 45 Gy in 1.8 Gy daily fractions; even with hyperfractionated WBRT to a lower total dose (36 Gy in 30 fractions twice daily), severe neurotoxicity appears to be merely delayed.[7,17] Nevertheless, favorable outcomes for patients who achieve CR or PR after completion of both chemotherapy and radiation have been observed in other studies.[23] Reducing the whole-brain dose while delivering a boost dose to the volume of PR in an effort to attain CR may be a reasonable compromise that is capable of reducing toxicity without sacrificing local control.

To date, there has been little enthusiasm for administering a boost to patients with PCNSL based on historical phase 2 data on patients treated either with radiation alone or radiation in combination with older chemotherapeutic regimens that had poor CNS penetration. In Radiation Therapy Oncology Group (RTOG) 83-15, there were high rates of failure at the original site of disease even after a boost to a total dose of 60 Gy.[1] Conversely, partial brain radiation has also been shown to result in a high rate (up to 49%) of relapse within the nonirradiated brain.[24] An improved CR rate to modern chemotherapy regimens presented an opportunity to de-intensify RT that is given to eliminate residual microscopic or radiographically undetectable disease. In more recent trials, patients with a CR to chemotherapy have been treated to a reduced WBRT dose without a boost to the original tumor volume with impressive rates of local control and OS.[8,19]

The potential role of reduced-dose WBRT after PR to MIC has not been widely investigated. In this exploratory analysis, there were 3 relapses in the PR group: 1 outside of the whole-brain field and 2 within the whole-brain field. One of the 2 in-field failures occurred at the site of original disease that was treated to a dose of 36 Gy, and this may have been prevented with a higher boost dose (to a final dose of 40-45 Gy). The second in-field failure occurred outside of the original extent of disease in the volume that received 23.4 Gy. Thus, although there were 3 relapses among the PR group of patients, only one recurrence (observed nearly 4 years after completion of radiation) could be hypothetically attributed to microscopic disease that was not eradicated with a dose of 23.4 Gy.

Although our study is not sufficiently powered to draw definitive conclusions, the relapse rates within the 23.4 Gy volume were intriguingly similar between patients who had either a PR or a CR to induction chemotherapy. With regard to toxicity, we did not find any significant difference in neurocognitive function before and after radiation for the 4 patients who received 23.4 Gy to the whole brain followed by a boost to residual disease. Although the neurotoxicity findings should be interpreted with caution given the limited amount of data available in our study, these findings suggest that utilizing 23.4 Gy to the uninvolved brain with a sequential boost to partially responded disease volumes could potentially reduce toxicity without sacrificing local control.

One patient with contrast-enhancing changes in the brain had biopsy-proven necrosis. This was a surprising finding because the patient had achieved a CR to 7 cycles of methotrexate-based chemotherapy followed by WBRT to 23.4 Gy in 1.8 Gy daily fractions. No boost dose was delivered. WBRT-induced necrosis has been linked to increased radiation dose, fraction size, and post-WBRT chemotherapy, but it is highly unlikely (<5% risk at 5 years) at doses <50 Gy when the radiation is administered in standard fraction sizes of ≤2 Gy.[25,26] In fact, methotrexate alone is also known to cause radiographic changes and neurotoxicity.[27-29] In the updated report of the phase 2 multicenter trial of rituximab, methotrexate, procarbazine, and vincristine followed by reduced-dose WBRT to 23.4 Gy, no severe late neurotoxicity was observed, but white matter changes on MRI scans reportedly increased.[8] Further follow-up and additional studies investigating reduced-dose RT after MIC (eg, RTOG 1114 [NCT01399372]) will be important to evaluate the risks of treatment-related necrosis after combined-modality therapy.

Little enthusiasm has been expressed for the administration of a boost to patients with PCNSL based on historical findings among patients who received WBRT as single-modality therapy followed by a boost to sites of

gross disease. The phase 2 RTOG 83-15 trial conducted in the 1980s involved treatment of 41 patients with WBRT to 40 Gy, followed by a 20-Gy boost. The median OS time in that study was only 11.6 months, and the predominant pattern of failure for more than half of the treated patients was at the original site of disease.[1] The authors of that study concluded that PCNSL, unlike other lymphomas, is not particularly radiosensitive.

On the other hand, completely omitting irradiation of radiographically uninvolved brain may be ill advised because initially uninvolved brain is at risk for disease relapse. In one study of 43 patients who received partial-brain RT for PCNSL to a median dose of 50 Gy, the 5-year in-field recurrence rate was 57% and the out-of-field brain recurrence rate was 49%; however, 40% of patients in that study did not receive systemic therapy, and those who did were treated mainly with cyclophosphamide, doxorubicin, vincristine, and prednisone–based regimens, which are known to be ineffective in PCNSL.[24] In the current study, the goal in administering a boost to persistent disease after reduced dose WBRT was to de-escalate therapy to the surrounding radiographically uninvolved brain, which theoretically could harbor only microscopic disease that could be eradicated with lower RT doses, particularly after MIC.

The few patients in this study with PD during MIC who were referred to radiation did not fare well, with a median OS time of only 3.4 months from the start of radiation. This short OS time is consistent with prior reports.[30] Refractory disease often does not respond well to radiation and, given the expected brief OS time for such patients, the value of definitive-intent high-dose radiation administered in conventional fraction doses of 1.8 to 3.0 Gy is questionable. Further investigation of alternate treatment strategies that can induce remission in such patients is needed. To date, single-agent nivolumab or ASCT have shown promise for inducing a response in such patients or for converting a PR to a CR.[31,32]

We acknowledge several limitations of this study. This is a single-institution study that spans several decades with a variety of treatment strategies, which makes generalizing these findings to other patient populations difficult. Our sample size is small within the study period, which severely limits our ability to draw definitive conclusions and also reflects a nontrivial degree of patient selection. Moreover, among PR patients who received 23.4 Gy to the whole brain followed by boost, only 4 patients underwent neurocognitive evaluations before and after radiation. Finally some pathologic analyses, such as molecular genetic testing, were not available.

Conclusions

Whole-brain dose reduction with a boost-dose escalation to residual disease for patients with a PR to MIC seems to be a reasonable treatment strategy with a favorable neurotoxicity profile that does not appear to compromise local control in carefully selected patients. For patients with PR to MIC, WBRT doses of 23.4 to 30 Gy to the whole brain may provide adequate control of microscopic disease without the toxicity associated with a full-dose regimen to 45 Gy. The optimal boost dose to the partially responding disease volume is unclear. With the proper treatment strategy, PR patients may benefit from reduced neurotoxicity and favorable outcomes similar to those of CR patients who receive de-intensified treatment strategies. These findings should be considered in future trial designs or in subsequent analyses of ongoing clinical trials.

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