Results of Whole-Brain Radiation As Salvage of Methotrexate Failure for Immunocompetent Patients With Primary CNS Lymphoma

Paul L. Nguyen, Arnab Chakravarti, Dianne M. Finkelstein, Fred H. Hochberg, Tracy T. Batchelor, and Jay S. Loeffler

ABSTRACT

Purpose
This study evaluates the efficacy and toxicity of whole-brain radiation therapy (WBRT) as salvage therapy for immunocompetent patients who failed initial high-dose methotrexate for primary CNS lymphoma (PCNSL).

Patients and Methods
The study cohort included 27 consecutive patients who failed initial high-dose methotrexate and then received salvage WBRT (median dose, 36 Gy). Actuarial survival was measured from the initiation of radiotherapy.

Results
Ten patients (37%) achieved a complete radiographic response (CR), and 10 patients (37%) a partial response to WBRT, for a 74% overall radiographic response rate. At the time of maximal response, Karnofsky performance status improved in 12 (44%) of 27 patients and at least stabilized in 67%. Median estimated survival from initiation of WBRT was 10.9 months (range, 0.3 to 63.7 months). The univariate predictor of longer survival was age less than 60 years at the time of WBRT ($P = .028$). Among patients who survived 4 months, achievement of a CR to WBRT by 4 months ($P = .002$) predicted longer survival. Late treatment-associated neurotoxicity was diagnosed in four patients (15%) and was significantly associated with total radiation doses greater than 36 Gy ($P = .04$). No patient treated with daily fractions less than 1.8 Gy developed late neurotoxicity.

Conclusion
For patients with PCNSL who experience treatment failure with methotrexate, WBRT provides high response rates (74%) and a median survival of 10.9 months. Age less than 60 years and response to WBRT predict post-WBRT survival. Modest rates of late neurotoxicity (15%) were seen and were associated with a total dose greater than 36 Gy.

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INTRODUCTION

Primary CNS lymphoma (PCNSL) currently accounts for almost 3% of newly diagnosed primary CNS tumors.$^{1,2}$ A multicenter phase II trial of whole-brain radiation therapy (WBRT) as primary therapy for PCNSL demonstrated a high initial response rate but a median survival of only 12 months.$^{3}$ Combination regimens of high-dose methotrexate (MTX)-based chemotherapy plus WBRT demonstrated improved median survival (36 to 60 months) compared with radiation alone, but they have been occasionally associated with delayed neurotoxicity, particularly in patients older than 60 years.$^{4-7}$ To minimize late neurotoxicity, several trials of high-dose MTX alone as initial therapy for PCNSL have
been conducted, and these suggest comparable survival with less long-term neurotoxicity compared with combination chemotherapy plus WBRT. As MTX-based chemotherapy has gained wider acceptance as initial therapy for PCNSL, WBRT is increasingly being used as salvage therapy. This study seeks to define the efficacy and toxicity of WBRT as a salvage therapy for patients who experience treatment failure with initial high-dose MTX for PCNSL.

**Patient Selection**

We studied 27 consecutive patients with biopsy-proven PCNSL who experienced treatment failure with initial treatment with high-dose MTX and subsequently received WBRT between 1994 and 2003. Failure was due to tumor relapse (10 patients) or progression of a refractory tumor (17 patients). Tissue diagnosis was based on a stereotactic biopsy (20 patients) or a partial resection (seven patients). All 27 patients had a diffuse large B-cell type of PCNSL. At diagnosis, CT scans of the chest, abdomen, and pelvis showed no evidence of extracranial spread, and all patients were human immunodeficiency virus seronegative. This study was approved by the hospital’s institutional review board and was in compliance with Health Insurance Portability and Accountability Act regulations. Baseline patient characteristics at diagnosis are listed in Table 1.

**Chemotherapy**

Patients received high-dose intravenous MTX (3.5 g/m² or 8 g/m²) as initial therapy. Each dose, adjusted for glomerular filtration rate, was infused over 4 hours. Therapy was generally scheduled as induction cycles every 14 days until complete response (CR), consolidation treatments every 14 days for two cycles, and maintenance treatments every 28 days for 11 cycles. Some patients who experienced treatment failure with MTX received alternate chemotherapies before WBRT, as described below.

**Radiation Therapy**

WBRT was delivered using opposed lateral beams to the level of the second cervical vertebra. Seven patients also received a boost dose to the gross tumor volume (five patients via involved-field radiation therapy and two patients via stereotactic radiosurgery [SRS]). For patients who did not receive a boost, the median WBRT dose prescribed was 36 Gy (range, 28 to 45 Gy). For the seven patients who received a boost, the median base dose was 36 Gy (range, 19.6 to 40 Gy), and the median boost dose for involved-field radiation therapy was 10 Gy (range, 10 to 21.6 Gy), whereas the SRS boost was given as 12 Gy or 16 Gy. The median daily fraction for WBRT was 1.8 Gy (range, 1.5 to 2.5 Gy), although the most common fraction size was 1.5 Gy (n = 10). During WBRT, 18 (67%) of 27 patients were maintained on oral corticosteroids, which were typically discontinued soon after WBRT.

### Table 1. Baseline Characteristics of Patients at Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
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<tr>
<td>Deep brain* involved</td>
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NOTE. All percentages are out of 27 patients, unless otherwise indicated. Abbreviations: KPS, Karnofsky performance status; CSF, cerebrospinal fluid. *Basal ganglia, brainstem, cerebellum, and periventricular lesions.

**Results**

### Response to MTX and Use of Other Pre-WBRT Chemotherapy

Overall, patients received a median of eight cycles of MTX before WBRT (range, three to 38 cycles). Ten patients...
(37%) achieved an initial CR to MTX after a median of 17 cycles, and 10 patients (37%) achieved an initial PR after a median of 6.5 cycles, for a 74% initial response rate to MTX. One patient (4%) had stable disease, and six patients (22%) continued to experience disease progression despite MTX.

The median time to MTX failure (measured from the start of the first dose) was 3.9 months (range, 0.4 to 41.8 months) for the entire cohort, 20.6 months (range, 10.1 to 41.8 months) for those who achieved a CR, and 3.3 months (range, 1.2 to 7.2 months) for patients who achieved a PR. Of the 10 patients who achieved an initial CR, eight patients received a second MTX induction course at the time of initial relapse, and four (50%) of those patients achieved a second CR on MTX. MTX was ultimately discontinued because of progression or recurrence in all patients.

Sixteen patients (59%) received additional chemotherapy after MTX failure and before WBRT. Specifically, seven patients received topotecan, four patients received cytarabine; three patients received temozolomide; one patient received procarbazine, carbamustine, and vincristine; and one patient received osmotic blood-brain barrier disruption followed by MTX, cyclophosphamide (Cytoxan; Bristol-Myers Squibb, Princeton, NJ) etoposide, and then cytarabine. Each eventually developed recurrent progressive disease prompting initiation of WBRT. The median duration between the initiation of these therapies and the start of WBRT was 3.2 months (range, 0.5 to 22.2 months).

**Baseline Characteristics at Initiation of WBRT**

Median age at initiation of radiation was 66.8 years (range, 34 to 84 years). Patients received their first radiation dose at a median of 5.7 months (range, 1.4 to 64.1 months) after initial diagnosis. Median Karnofsky performance status (KPS) was 70 (range, 30 to 100) at baseline (Table 2).

### Table 2. Baseline Characteristics of Patients at Initiation of WBRT

<table>
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<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
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<tr>
<td>Age &gt; 60 years</td>
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<td>63</td>
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<tr>
<td>KPS ≥ 70</td>
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<td>Multiple lesions</td>
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<td>Deep brain* involved</td>
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<td>Range</td>
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<td>MTX stopped for relapse</td>
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<tr>
<td>Additional therapy before WBRT</td>
<td>16</td>
<td>59</td>
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</table>

NOTE. All percentages are out of 27 patients. Abbreviations: WBRT, whole-brain radiotherapy; KPS, Karnofsky performance status; MTX, methotrexate. *Basal ganglia, brainstem, cerebellum, and periventricular lesions.

**Radiographic Response to Radiation**

After WBRT, 10 patients (37%) achieved a best response of CR, and 10 patients (37%) achieved a best response of PR, for a total response rate of 74%. Median time to maximum response for patients who achieved a CR was 2.5 months (range, 0.9 to 9.2 months), and the median time to maximum response for patients who achieved a PR was 1.5 months (range, 0.8 to 4.6 months). Seven patients (26%) remained stable or experienced disease progression during WBRT. The radiographic response rate to WBRT was similar for patients whose disease was recurrent on MTX versus refractory to MTX (70% v 76%, respectively) and was not significantly different for those who had received post-MTX salvage therapies before WBRT versus those who had not (63% v 91%; P = .18, Fisher’s exact test), or for those who received corticosteroids during radiation versus those who did not (67% v 89%; P = .36).

All patients completed their prescribed course of WBRT except for two patients (7%) who deteriorated clinically during WBRT. Both stopped treatment after 9 Gy and died from their disease within 5 days.

**Progression-Free Survival and Recurrences**

Median progression-free survival (PFS) from the start of radiation was 9.7 months (range, 0.3 to 57.6 months). Median PFS was 57.6 months for patients who achieved a CR and 9.7 months for people who achieved a PR.

Of the 20 patients who achieved a CR or PR after WBRT, eight patients subsequently developed radiographic evidence of progression or recurrence at a median of 18.8 months after WBRT. Four patients (50%) experienced progression in the brain alone, and four patients (50%) developed extra-cranial recurrences without evidence of progression within the CNS. Specifically, one patient had hepatic and renal metastases, one experienced treatment failure in the right breast, one experienced treatment failure in bilateral adrenal glands, and one developed diffuse systemic nodal metastases.

**Salvage Therapies After WBRT**

Seven patients (26%) received additional therapy after WBRT. Six received salvage chemotherapy at the time of progression or relapse after WBRT, and one received consolidation therapy immediately after achieving a CR as a result of WBRT.

Three patients received temozolomide as their sole salvage therapy. Two patients who experienced treatment failure systemically received cyclophosphamide, doxorubicin, vincristine, and prednisone. One patient received topotecan and then experienced treatment failure systemically in diffuse lymph nodes and received cyclophosphamide, doxorubicin, vincristine, and prednisone, then rituximab (Rituxan; Genentech, South San Francisco, CA), and then cytarabine. Finally, one patient who received SRS later received rituxan and temozolomide.
These seven patients had a median survival of 37.2 months, but there were not enough comparison patients alive at the time of salvage therapy to perform a landmark analysis to determine whether salvage therapy improved survival or whether the administration of salvage therapy was merely a marker for overall health status.

**Overall Survival After WBRT**

Of the 20 patients who died in this cohort, 17 patients died as a result of PCNSL, two patients died at an outside facility with cause of death unknown, and one patient who had B-cell type PCNSL died from metastasis of an unrelated extracranial T-cell lymphoma. Median estimated survival from the start of radiation was 10.9 months (range, 0.3 to 63.7 months). The estimated survival at 12 months was 49%, and the estimated survival at 24 months was 40%. (Fig 1).

Age more than 60 years at time of WBRT was a significant predictor of post-WBRT survival ($P = .028$). Twelve-month post-WBRT survival in patients younger than 60 years versus age older than 60 years was 67% versus 39%, respectively, as shown in Figure 2. Median survival for patients younger than 60 years was 37.2 months, compared with a median survival of 7.3 months for patients older than 60 years of age.

For patients who achieved a CR, PR, or neither, median survival from the start of WBRT was 63.7 months, 10.9 months, and 2.4 months, respectively. Using a landmark analysis to remove response-time bias, response to WBRT was shown to be a significant predictor of survival. At the landmark time of 4 months after the start of WBRT, eight patients had already died and were excluded from the analysis. For the remaining 19 patients, response at the landmark time was CR in eight patients, PR in eight patients, and neither in three patients. Median actuarial survival from the landmark time for CR, PR, and neither was 59.7 months, 18.6 months, and 2.4 months, respectively ($P = .002$, log-rank test), as shown in Figure 3.

Post-WBRT survival was not affected by preradiation KPS, the number of contrast-enhancing masses, whether the disease was recurrent versus refractory to MTX, whether there was deep-brain involvement, whether a boost was used, whether corticosteroids were used during WBRT, or the total dose administered.

**Acute and Long-Term Radiation Toxicity**

The most common side effect noted during WBRT was fatigue. Only one patient (4%) developed acute cerebral edema, which occurred after 5 days of treatment. It is unclear whether this was due to radiation effects or tumor progression.

Median KPS at the time of maximum response to WBRT was 70 (range, 10 to 100), which was unchanged from the median preradiation KPS (range, 30 to 100). KPS improved in 12 patients, remained the same in six patients, and decreased in nine patients. At the time of maximum response to radiation, 19 patients (70%) were able to walk
independently, one patient (4%) was able to walk with assistance, and seven patients (26%) were nonambulatory. Before WBRT, only two of the eight patients who had held jobs before diagnosis were still working. After radiation, both patients remained actively employed, and one additional patient was able to return to the work force.

Three patients (11%) developed definite treatment-related delayed neurotoxicity, and one patient (4%) developed probable delayed neurotoxicity. Late neurotoxicity was diagnosed at a median of 25 months (range, 7.2 to 33.2 months) after the start of WBRT. The three definite cases developed subcortical symptoms with MRI evidence of treatment-related white matter disease and had no radiographic evidence of tumor progression. Specifically, one patient developed gait difficulty and impaired short-term memory at 17.9 months after WBRT. A second patient developed memory difficulties and parkinsonian symptoms at 32 months after WBRT, which responded well initially to carbidopa/levodopa. A third patient developed gait instability and loss of bladder control at 33.2 months after WBRT.

The patient with probable late neurotoxicity had evidence of subcortical symptoms that were most likely related to WBRT, but which also had an alternate possible cause. Specifically, the patient developed progressive confusion and lethargy at 7.2 months after WBRT and had MRI evidence of extensive radiation-related white matter disease at the time of the symptoms. However, this patient was also simultaneously showing radiographic evidence of progression of disease.

None of the patients who received a total dose $\leq$ 36 Gy developed treatment-related neurotoxicity, compared with 31% of those who received a dose greater than 36 Gy ($P = .04$, Fisher’s exact test). Late toxicity occurred in no patient whose fraction size was equal to 1.5 Gy, compared with 27% of those who had a higher fraction size, but this difference was not significant ($P = .26$). In addition, late neurotoxicity occurred in none of the patients who were under 60 years old at the time of radiation, compared with 24% of the patients who were more than 60 years old at the time of radiation, but this difference was also not significant ($P = .26$).

**Overall Survival From Date of Diagnosis**

Median overall survival for all patients from the date of diagnosis was 29.5 months (range, 2.0 to 83.8 months). Estimates of overall survival at 36 and 48 months are 43% and 26%, respectively, as shown in Fig 4.

**DISCUSSION**

The results above suggest that for patients with PCNSL who experience treatment failure with initial MTX, WBRT is an effective salvage therapy with modest toxicity. The observed response rate to WBRT of 74% (37% CR + 37% PR) compares favorably with the 63% response rate (39% CR + 24% PR) reported in Radiation Therapy Oncology Group 85-13 for patients whose initial therapy was WBRT. This suggests that the development of MTX-resistant disease does not decrease radioresponsiveness, which supports the use of WBRT after MTX failure.

The post-WBRT median survival of 10.9 months is also comparable to the 11.6 months previously reported in the literature for patients treated with initial WBRT, suggesting that post-WBRT survival is not diminished in MTX-resistant disease. Although it is not possible without a control group to prove that the WBRT was responsible for this survival, both newly diagnosed and recurrent PCNSL has a median survival of only 1.5 to 2 months if left untreated. Therefore, WBRT most likely confers a true survival benefit, especially for patients who achieve an initial CR after WBRT.

Because 26% of patients in this study received additional salvage therapy after WBRT, it is theoretically possible that salvage therapies were the main contributors to survival. However, only one patient received salvage therapy before progression, and the median PFS was 9.7 months, which was only slightly less than the median post-WBRT survival of 10.9 months. In addition, Figure 1 shows that the overall and PFS curves are nearly superimposable. Therefore, the majority of the additional survival time after WBRT is in the absence of salvage chemotherapy.

Our finding that age less than 60 years is associated with better post-WBRT survival is consistent with a prior study. In addition, a landmark analysis showed that the achievement of a CR after salvage WBRT prolongs survival.

One major goal in delaying radiation until MTX failure rather than giving combination radiation and chemotherapy up front is to reduce the incidence of treatment-associated delayed neurotoxicity. This study found evidence of delayed neurotoxicity in four (15%) of 27 patients, which
was not substantially different from the 15% to 32% previously reported for patients who received combination chemotherapy plus WBRT. Among patients with age greater than 60 years, the incidence of delayed neurotoxicity was 24%, which is substantially lower than the up to 90% incidence reported for this age after receiving combination chemotherapy and radiation. It is possible, then, that delaying WBRT for this age group can result in lower treatment-associated neurotoxicity. However, it should also be acknowledged that an alternate explanation for the apparently low incidence of neurotoxicity is that many patients older than 60 years of age may not have survived long enough after WBRT to develop delayed neurotoxicity.

In the largest of the studies of combination chemotherapy and radiation, eight (67%) of the 12 patients who developed neurotoxicity died as a result of this complication, whereas none of the four patients who developed late neurotoxicity in the current study died from this complication. Specifically, three patients later died of tumor recurrence, and one patient developed treatment-related parkinsonism that improved with carbidopa/levodopa and is still alive 18 months after neurotoxicity was diagnosed. Therefore, it may be possible that the neurotoxicity that results from delayed radiation after MTX failure is less severe than what typically results from combination chemotherapy and radiation.

This study also found that a total radiation dose greater than 36 Gy is associated with a higher frequency of delayed neurotoxicity (P = .04). Although the results for fraction size were not significant, it is notable that none of the patients who received 1.5 Gy per day developed neurotoxicity. Fraction sizes of 1.8 Gy or 2.0 Gy are more typical, but because fraction size is generally thought to be a contributor to late neurotoxicity, it is currently standard practice at our institution to use the reduced fraction size of 1.5 Gy per day and treat to a total dose of 36 Gy.

A prior study of combination chemotherapy plus WBRT demonstrated a strong association between age greater than 60 years and late neurotoxicity, and although this study may not have been adequately powered to detect a difference, all four cases of late neurotoxicity in the study occurred in patients older than 60 years of age.

A prior meta-analysis of 92 patients treated primarily with WBRT alone found that the overwhelming majority (93%) failed in the CNS and that only 7% had isolated systemic recurrences in the absence of CNS disease. Of the eight patients who experienced disease progression in this study after an initial response to WBRT, 50% failed in the CNS alone and 50% failed systemically without CNS progression, possibly reflecting a difference in patterns of failure between patients treated with WBRT versus WBRT + MTX.

This study is limited by its sample size and there may not have been adequate power to identify many important prognostic factors for survival. In addition, it is important to note that among all patients with PCNSL who receive initial MTX, the subset that goes on to receive WBRT for failure is a highly selected sample. For example, the median time to failure of MTX was 3.9 months for the study cohort, whereas the median time to failure of MTX for an unselected group of 54 patients who were initially treated with high-dose MTX for PCNSL at Massachusetts General Hospital from 1987 to 2002 was 26 months. This difference is also reflected in a median overall survival from diagnosis of only 29.5 months in our study cohort compared with approximately 102 months noted for the entire cohort of PCNSL patients on MTX. Ideally, it would be best to know what the response rate and post-WBRT survival would be if all patients who experienced treatment failure with MTX for PCNSL received WBRT, rather than only the earliest failures, as occurred in this study. This would provide a more accurate description of the efficacy of WBRT as a salvage for PCNSL. Finally, treatment-related neurotoxicity may sometimes have subtle signs that can be missed on clinical examination, and therefore it is possible that subacute neurotoxicity was underdiagnosed.

Despite the limitations discussed, this study may be the first to evaluate the efficacy of WBRT as a salvage therapy for patients who experienced treatment failure with initial MTX therapy for PCNSL. The data presented here suggest that WBRT is an effective salvage therapy that results in a high response rate, median survival of approximately 11 months, and a relatively modest rate of late nonfatal neurotoxicity. Further studies will be needed to validate these results in a larger cohort of patients.

Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES


