Salvage radiotherapy in patients with recurrent or refractory primary or secondary central nervous system lymphoma after methotrexate-based chemotherapy

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Background: To assess the efficacy of salvage radiation therapy (RT) in patients with recurrent/refractory primary or secondary central nervous system lymphoma (CNSL) after initial methotrexate (MTX)-based chemotherapy and to identify factors associated with treatment outcome.

Patients and methods: We reviewed 36 patients with primary or secondary CNSL who relapsed after MTX therapy and received salvage RT. Primary end points were radiographic response and overall survival (OS).

Results: After salvage RT, 18 patients (50%) achieved a complete radiographic response and 6 (17%) achieved a partial response, for an overall response rate of 67% [95% confidence interval (CI) 49% to 81%]. The median OS from start of salvage RT was 11.7 months (range: 0.6–94.7). Patients treated with less than five cycles of MTX before failure had a significantly shorter OS than patients who received five or more cycles (9.2 months versus not reached, P = 0.04). Patients with CNSL limited to brain only had a significantly longer OS than patients with disease in the brain and other central nervous system locations (16.5 versus 4.5 months, P = 0.01).

Conclusion: Salvage RT is effective for patients with recurrent/refractory primary or secondary CNSL after initial MTX therapy. Having received five or more cycles of MTX before failure and CNSL limited to the brain at relapse are associated with longer OS.

Key words: CNS, high-dose methotrexate, lymphoma, radiotherapy, salvage

introduction

Primary central nervous system lymphoma (PCNSL) is a rare aggressive tumor that currently accounts for almost 3% of newly diagnosed primary brain tumors in the United States [1]. While PCNSL is sensitive to both chemotherapy and radiation therapy (RT), the optimal treatment for PCNSL remains controversial. Median survival after whole-brain RT as primary therapy is only 11.6 months [2]. Combined modality therapy using high-dose methotrexate (MTX) and whole-brain RT is associated with more favorable results, with median survival times ranging from 36 to 60 months. However, particularly for patients over the age of 60 years, there is a significant risk of delayed treatment-related neurotoxicity [3–9]. A recent prospective trial showed that in patients with a complete response (CR) to high-dose MTX and immunotherapy, low-dose whole-brain RT resulted in an excellent treatment outcome with preservation of neurocognitive function even among older patients [10]. Others have advocated the use of MTX-based chemotherapy, deferring RT until disease progression or relapse [11–13].

Secondary central nervous system lymphoma (CNSL) is a rare manifestation of systemic non-Hodgkin’s lymphoma, with one study showing a cumulative incidence of 2.8% central nervous system (CNS) relapse in patients with systemic aggressive non-Hodgkin’s lymphoma and a median survival of only 2.2 months after diagnosis of the CNS disease [14]. The use of high-dose MTX in patients with secondary CNSL is associated with a significantly longer survival time [15].

Despite promising results with the use of high-dose MTX-based chemotherapy for both primary and secondary CNSL, a significant proportion of patients will experience refractory or relapsed disease. Limited data are available on salvage options in these patients. In this study, we sought to determine the efficacy of RT as salvage therapy in patients with refractory or recurrent primary or secondary CNSL after MTX failure and to assess factors associated with salvage outcome.

methods

We retrospectively reviewed the records of patients with primary or secondary CNSL who received initial MTX therapy but had tumor progression or...
recurrence and received salvage RT at Dana-Farber/Brigham & Women’s Cancer Center between 1997 and 2009. CNSL was defined as disease involving the brain parenchyma, spinal cord, leptomeninges, or orbits. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board with a waiver of informed consent.

Primary end points were radiographic response to RT and overall survival (OS) after salvage RT. Radiographic response was evaluated with non-gadolinium-enhanced magnetic resonance imaging using standardized response criteria [16]. Specifically, CR was defined as complete resolution of abnormal contrast enhancement. Partial response (PR) was defined as a reduction in size of >50% of the contrast enhancement. Progression of disease was defined as unequivocal growth of >25% or development of a new lesion. All other responses were considered stable disease. OS was defined as the time from start of RT until death or the date last known alive.

Statistical analysis was performed using Microsoft Office Excel (version 2007) and SAS (version 9.2). Exact binomial confidence intervals (CIs) were used to describe response to salvage RT. The method of Kaplan and Meier was used to characterize OS. The log-rank test was used to compare survival curves.

To assess clinically significant delayed neurotoxicity, in our medical record review, we specifically searched for documentation of impaired short-term memory, gait instability, and bladder/bowel incontinence in the absence of clinical recurrence or progression.

results

Patient and initial treatment characteristics

We identified 36 patients with refractory or recurrent primary (n = 15) or secondary (n = 21) CNSL after initial MTX-based chemotherapy who received salvage RT. The median age at CNSL diagnosis was 55.5 years (range: 20–83). Among the 21 patients with secondary CNSL, the median time from diagnosis of the primary lymphoma to diagnosis of the secondary CNSL was 5.9 months (range: 0–319). Twenty-two patients were male (61%) and 14 were female (39%). Histologies included diffuse large B-cell lymphoma in 33 patients (92%), marginal zone lymphoma in 2 (6%), and mantle cell lymphoma in 1 (3%). Sites of involvement included brain parenchyma in 28 patients (78%), including 1 with concomitant spinal cord disease and 1 with concomitant ocular lymphoma; spinal cord only in 4 (11%); and leptomeninges only in 4 (11%). Nineteen patients (53%) had multiple CRL lesions; 9 (25%) had deep brain lesions (basal ganglia, brainstem, cerebellum, and periventricular lesions); and 10 (28%), excluding those with leptomeninges-only disease, had positive cerebrospinal fluid cytology. Thirty-three patients (92%) were immunocompetent, 2 (6%) were human immunodeficiency virus seropositive, and 1 (3%) was immunosuppressed after renal transplant. Baseline patient characteristics are summarized in Table 1.

At diagnosis of the primary or secondary CNSL, 33 patients (92%) received high-dose MTX in a median dose of 3.5 g/m² (range: 2.3–6.5) for a median of four cycles (range: 1–15). The remaining three patients received intrathecal MTX only, for a median of 10 doses (12 mg). Of the patients who received high-dose MTX, 13 also received intrathecal MTX.

Response to initial treatment

After initial MTX therapy, five patients (14%) had an initial CR, six (17%) had a PR, and six (17%) had stable disease. The median time to MTX failure (measured from the start of the first dose) was 22.4 months (range: 9.0–55.7) for patients who achieved a CR and 2.9 months (range: 2.2–9.0) for patients who achieved a PR. Nineteen patients (53%) experienced disease progression after a median of four cycles of MTX (range: 2–8). A total of six patients (17%) received additional salvage systemic therapy before referral for salvage RT.

Salvage radiotherapy

Salvage RT consisted of whole-brain RT delivered using opposed lateral beams in 33 patients (92%). Of these, the nasopharynx was included in the treatment field in one patient. Seven patients received a boost dose to the gross tumor volume. The median whole-brain RT dose for patients who did not receive a boost was 40 Gy (range: 14–45) with median daily fractions of 2 Gy (range: 1.7–3). For patients who received a boost, the median whole-brain RT dose was 36 Gy (range: 24–44) with a median daily fraction of 2 Gy (range: 1.6–2), and the median boost dose was 10 Gy (range: 3–19). Of the 33 patients who received whole-brain RT, 6 (17%) received additional RT to the spine at a median dose of 31.2 Gy (range: 14–40) in median daily fractions of 1.8 Gy (range: 1.6–2.0). Three patients did not receive whole-brain RT. Two of those received RT...
isolated to the bilateral orbits at a dose of 36 Gy, and one received RT to the spine only at a dose of 40 Gy.

**Outcome after salvage radiotherapy**

After salvage RT, 18 patients (50%) achieved a CR and 6 (17%) achieved a PR, for an overall response rate of 67% (95% CI 49% to 81%). One patient (3%) had stable disease, 10 (28%) progressed, and 1 patient died as a result of a fall before response assessment (Table 2). Of the 24 patients with a CR or PR, 13 (54%) developed radiographic evidence of recurrence at a median of 7.4 months (range: 0–31.9) after salvage RT. Three patients relapsed at the original site, seven relapsed at new sites in the CNS, and three developed non-CNS recurrence. Median time to CNS-only relapse was 7.9 months (range: 2.8–31.9). Seven patients underwent high-dose therapy with stem-cell rescue either immediately after completing salvage RT or at the time of further recurrence. Two of these seven are disease-free at a median of 42.5 months. Ten patients received additional salvage RT after further CNS recurrence, 9 of whom progressed despite treatment. Of the patients who progressed after additional RT, five received stereotactic radiosurgery, two received whole-spine RT, and two received palliative RT to localized areas of the spine.

The median follow-up time was 43.1 months (range: 4.9–79.8). One patient was lost to follow-up 22.2 months after salvage RT, at which time he was disease free. This patient remains alive at 94.6 months, although his current disease status is unknown. The 2-year actuarial OS was 32% (95% CI 19% to 46%) (Figure 1). The median OS from the start of salvage RT was 11.7 months (range: 0.6–94.7) and 44% were alive 1 year after the start of RT. At the time of analysis, 24 patients in our cohort had died; the cause of death was progressive lymphoma in 22 patients, cerebrovascular accident in 1, and 1 patient died as the result of a fall 5 days after completing RT. Of the 12 patients still alive, 11 were in complete remission from CNSL and 1 was in hospice. Of note, eight patients (22%) are alive and disease free beyond 3 years after salvage RT, with a median OS of 57.9 months (range: 42.9–94.7).

Factors potentially associated with length of OS were assessed. Patients who received five or more cycles of MTX prior to relapse had a significantly longer OS than patients who received less than five cycles (median not reached versus 9.2 months, \( P = 0.04 \)) (Figure 2). Patients with CNSL limited to brain only had a significantly longer OS than patients with disease in the brain and extracranial CNS sites (16.5 versus 4.5 months, \( P = 0.01 \)) (Figure 3). Age at initial diagnosis, age at CNSL diagnosis, gender, primary versus secondary CNSL, multiple CNS lesions versus single lesion, and refractory versus recurrent disease were not associated with OS (Table 3).

**Toxicity**

Documentation of neurotoxicity was available for 20 patients. Of these, seven patients (35%) experienced neurotoxicity including short-term memory deficit, gait instability, confusion, and/or visual/hearing impairment in the absence of clinical recurrence or progression. Of note, five of these seven patients had documented baseline neurological deficit prior to initiation of salvage RT, including short-term memory deficits, gait instability, and visual symptoms. Two of the seven patients (29%) with neurotoxicity after salvage RT were ≥60 years of age at the time of RT.

**Discussion**

The results of this study suggest that salvage RT is effective for patients with recurrent or refractory primary or secondary CNS lymphoma after initial MTX therapy. The observed response rate to RT of 67% and the median OS after salvage RT of 11.7 months are comparable to the 63% response rate and median OS of 11.6 months observed when whole-brain RT alone was used as initial treatment for PCNSL [2]. These results suggest that CNSL remains responsive to radiotherapy after the use of MTX and that survival after RT is not diminished in MTX-resistant disease.

Others have evaluated the efficacy of whole-brain RT as salvage therapy in patients with PCNSL that relapsed after initial high-dose MTX. In one study of 27 patients with MTX failure, the overall radiographic response rate with salvage whole-brain RT was 74%, with a median survival from initiation of whole-brain RT of 10.9 months (range: 0.3–63.7). Age <60 years at the time of RT and achieving a CR to whole-brain RT were associated with a significantly higher median OS [7]. In a study from Memorial Sloan-Kettering Cancer Center on 48 patients with refractory or recurrent PCNSL, salvage whole-brain RT resulted in an overall response rate of 79% and a median survival time of 16 months from the start of RT [8]. As in the previous study, younger age and achieving a CR to salvage RT were favorable prognostic factors. Silvani et al. [13] reported on their experience of 36 patients with PCNSL treated with MTX-based chemotherapy and deferred RT. Twenty-seven patients subsequently received whole-brain RT either due to lack of response or due to relapsed disease after MTX. The median progression-free survival time after salvage RT was 10.5 months. Details on patterns of failure and prognostic factors, however, were not available [13]. Phase II studies have been conducted evaluating the use of MTX-based chemotherapy alone as first-line therapy for PCNSL, deferring RT until the time of relapse. The outcome of salvage RT in these patients, however, was not reported [11, 12].

Our findings of an overall radiographic response rate of 67% and a median OS from the time of salvage RT of 11.7 months

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**Table 2.** Radiographic response after salvage RT

<table>
<thead>
<tr>
<th>Response</th>
<th>( n )</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>18</td>
<td>50.0</td>
<td>32.9% to 67.1%</td>
</tr>
<tr>
<td>Partial response</td>
<td>6</td>
<td>16.7</td>
<td>6.4% to 32.9%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>2.8</td>
<td>0.1% to 14.5%</td>
</tr>
<tr>
<td>Progression</td>
<td>10</td>
<td>27.8</td>
<td>14.2% to 45.2%</td>
</tr>
<tr>
<td>Unevaluable*</td>
<td>1</td>
<td>2.8</td>
<td>0.1% to 14.5%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One patient died before response assessment.

RT, radiation therapy; CI, confidence interval.
are consistent with previous findings. Unlike previous studies, the current study includes patients with secondary CNSL, a rare occurrence in patients with systemic non-Hodgkin’s lymphoma. In a study of 113 patients with isolated secondary CNSL, age < 60 years ($P = 0.006$) and MTX ($P = 0.008$) as initial treatment for the secondary CNSL were significantly associated with longer survival [15]. However, to date, there is a lack of data on salvage options for patients with secondary CNSL who experience a relapse after MTX therapy. In this study, the median OS of patients with secondary CNSL from the start of salvage RT was 8.6 months, and the type of CNSL (primary versus secondary) was not a significant predictor of survival. This suggests that, in patients with PCNSL, salvage RT is a reasonable approach in patients with secondary CNS lymphoma with MTX failure.

This study identified new factors that are significantly associated with survival in this population with MTX-resistant disease, including previous treatment with five or more cycles of MTX ($P = 0.04$) and CNS disease isolated to the brain parenchyma ($P = 0.01$). The finding of longer survival in patients who had received a higher number of cycles of MTX prior to relapse is likely due to the poor prognosis of patients who progress shortly after initiation of MTX and also a higher chance of salvage in the more robust patients who were able to complete a full course of chemotherapy. Half of the patients in this cohort had CNS disease involvement outside of the brain at relapse, and their median survival time was significantly lower, at only 4.5 months. Our findings suggest that it may be reasonable to consider a more abbreviated course of palliative RT in these patients with limited life expectancy.
Previous studies have shown that age <60 years is associated with longer survival after whole-brain RT [2, 7, 8]. In this study, age was not associated with survival, which may be related to the fact that only 25% of our patients were ≥60 years of age.

This study is limited by its retrospective nature with potential selection bias. Treatment regimens, from chemotherapy prior to MTX to additional salvage therapies, were not uniform, in part reflective of the lack of consensus regarding the optimal management for patients with primary or secondary CNSL. The small sample size also resulted in limited power to identify predictive factors for survival and ability to control for confounding factors. Our report on treatment-related neurotoxicity was largely descriptive in nature and, as in most other retrospective series, there were no baseline evaluations or use of standardized instruments to measure neurocognitive impairment.

Despite these limitations, this study confirms the important role of salvage radiotherapy in patients with MTX-resistant disease for primary or secondary CNSL, with a subset of patients remaining disease free beyond 3 years after salvage therapy. A larger study with formal neurocognitive evaluation may help identify patients who may benefit the most from this form of salvage therapy.

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**Disclosure**

The authors declare no conflict of interest.

**References**


