Review

Treatment of Relapsed Central Nervous System Lymphoma with High-Dose Methotrexate

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ABSTRACT

Purpose: Over the past decade, high-dose methotrexate has emerged as the single most effective agent in the initial treatment of primary nervous system lymphoma. However, the majority of patients who respond initially to treatment relapse. The optimal management of these patients has not been determined. We performed a multicenter, retrospective study of high-dose methotrexate in patients with relapsed central nervous system lymphoma.

Experimental Design: Patients with relapsed disease were eligible if they achieved a complete response to initial treatment with methotrexate-based chemotherapy or received methotrexate after gross total resection or interstitial radiation. All of the patients were retreated with a regimen containing high-dose methotrexate (≥3 g/m²).

Results: Twenty-two patients with a median age of 58 years were included in the study. Overall response rates were 91% to first salvage (20 of 22 patients) and 100% to second salvage (4 of 4 patients). Median survival was 61.9 months after first relapse (95% confidence interval, 42.1–∞) and 91.9 months overall (95% confidence interval, 47.2–∞). Toxicity was primarily hematologic with 10 episodes of grade 3 or 4 toxicity during 566 cycles of chemotherapy.

Conclusions: These results indicate that high-dose methotrexate remains effective for relapsed central nervous system lymphoma in patients who initially respond to methotrexate and raise the possibility of deferring more toxic salvage regimens in this select group of patients.

INTRODUCTION

The introduction of high-dose methotrexate (HD-MTX) into the treatment of primary nervous system lymphoma has substantially improved the survival of patients with this disease (1–3). Between 50 and 65% of patients achieve a complete radiographic response after treatment with regimens containing HD-MTX, and an additional 20 to 35% of patients achieve a partial radiographic response (4–7). Complete responses (CRs) are not durable in most patients, and the majority subsequently relapse (4–7). In addition, 10 to 15% of patients have lymphoma refractory to first-line therapy. The prognosis for patients with relapsed or refractory central nervous system (CNS) lymphoma is poor. Without treatment, median survival is 2 months (8).

Small series of cases of treatment for relapsed or refractory primary nervous system lymphoma have been published (9–14). Salvage chemotherapy extends survival compared with no therapy but the number of long-term survivors is small. New approaches to the treatment of relapsed and refractory disease are needed. We report a retrospective evaluation of patients with recurrent primary nervous system lymphoma treated with high-dose intravenous MTX at four institutions.

PATIENTS AND METHODS

Patients. The records of immunocompetent patients with CNS lymphoma treated between 1996 and 2003 at Massachusetts General Hospital, Johns Hopkins University, University of Alabama at Birmingham, and Wake Forest University School of Medicine were reviewed. All of the patients had pathologically confirmed non-Hodgkin’s lymphoma, involving the brain parenchyma, vitreous fluid, and/or cerebrospinal fluid (CSF). Patients who were treated with MTX-based chemotherapy as first-line treatment were assessed for response to treatment. Those who achieved a CR to therapy, defined as resolution of contrast-enhancing tumor after initial treatment, were included in the study. A subset of patients who received MTX-based chemotherapy after gross total resection or interstitial radiation was also included in the study. The evaluation of patient records was approved by the institutional review board (IRB) at Massachusetts General Hospital.

Treatment. The administration of HD-MTX has been described in detail elsewhere (5). Patients received hydration with oral or intravenous sodium bicarbonate until urine output exceeded 100 mL/h and urine pH exceeded 7.0. Intravenous MTX (≥3g/m²) was administered with 1:1 dose reduction for each point of glomerular filtration rate below 100 mL/min. For example, a patient with a glomerular filtration rate of 85 received a 15% dose reduction. Patients with glomerular filtration rate <50 mL/min were excluded from receiving MTX. Urine output greater than 100 mL/h and urine pH >7 were maintained until MTX was adequately cleared from the serum. Rescue with
leucovorin calcium was initiated 24 hours after the start of MTX infusion and continued until MTX was cleared.

Response to chemotherapy was monitored by contrast-enhanced cranial magnetic resonance imaging for parenchymal disease, by CSF cytology for leptomeningeal disease, by slit-lamp examination with or without vitreal biopsy for intraocular lymphoma, and by contrast-enhanced spinal magnetic resonance imaging for neurolymphomatosis. Time between evaluations was determined by the treating physician. Response to treatment after reinduction was defined as CR if there was complete resolution of the enhancing tumor without evidence of ocular or leptomeningeal disease, mixed response if there was a CR in brain parenchyma but persistent disease in the eyes, partial response if there was at least a 50% reduction in the volume of enhancing tumor, and progressive disease if there was an increase in the size of enhancing tumor or the appearance of new lesions. All other responses were defined as stable disease.

Patients were treated every 2 weeks until they achieved a CR in brain without evidence of ocular or nerve disease, achieved a partial response but failed to improve with continued therapy, or experienced progressive disease. Those who achieved a CR were then treated monthly for a period of time determined by the treating physician.

**Statistical Considerations.** Time to relapse was defined as the interval of time between documentation of CR after initial treatment to documentation of relapsed disease. Patients were assigned multiple times to relapse (treatment to documentation of relapsed disease). Patients were treated with MTX-based chemotherapy on relapse. There were 13 males and 9 females with a median age of 58 years. Previous medical histories included testicular non-Hodgkin lymphoma in remission (three patients), rheumatoid arthritis (one patient), immune thrombocytopenic purpura (one patient), and recur-

The primary end points in this analysis were best radiographic response after salvage therapy, time to death from initial CNS diagnosis, and time to death from first salvage. Time to death from initial CNS diagnosis is a left-truncated event time, because it necessarily precedes the time to death or last follow-up. The Kaplan–Meier method was used to estimate curves for overall survival and survival after relapse. Cox proportional-hazards models were fitted to estimate hazard ratios and to perform regression analysis. The estimation and regression analyses were adjusted for truncation where necessary. Age and ocular involvement were used as predictors in univariate regression models for each of the endpoints.

Number of cycles of chemotherapy until initial response, time to initial response, and time to first relapse were used as predictors of second response, time to second relapse, and time to death from initial relapse. The number of cycles of chemotherapy until second response was used in the analysis of time to second relapse.

**RESULTS**

The records of patients with relapsed CNS lymphoma at the four participating institutions were reviewed. Twenty patients had achieved a CR after initial MTX-based therapy. Two patients had no evidence of residual disease after gross total resection or interstitial radiation and received MTX (Table 1). All of the patients were treated with MTX-based chemotherapy on relapse. There were 13 males and 9 females with a median age of 58 years. Previous medical histories included testicular non-Hodgkin’s lymphoma in remission (three patients), rheumatoid arthritis (one patient), immune thrombocytopenic purpura (one patient), and recur-

### Table 1. Patient characteristics and initial treatment with MTX

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>Extent of disease</th>
<th>Initial MTX regimen</th>
<th>Cycles to CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80/M</td>
<td>Brain</td>
<td>HD-MTX*</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>35/F</td>
<td>Brain</td>
<td>HD-MTX</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>78/M</td>
<td>Brain</td>
<td>HD-MTX</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>64/M</td>
<td>Brain</td>
<td>HD-MTX</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>52/F</td>
<td>Brain</td>
<td>HD-MTX → SRS</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>62/F</td>
<td>Brain</td>
<td>HD-MTX → WBRT</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>40/F</td>
<td>Brain</td>
<td>HD-MTX</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>67/M</td>
<td>Brain + nerve</td>
<td>HD-MTX</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>50/F</td>
<td>Brain + ocular</td>
<td>HD-MTX</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>72/F</td>
<td>Brain + ocular</td>
<td>CHOD → M-CHOD</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>62/M</td>
<td>Brain + CSF</td>
<td>M-CHOD</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>31/F</td>
<td>Brain → ocular</td>
<td>Ocular RT → HD-MTX</td>
<td>4</td>
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<tr>
<td>13</td>
<td>60/M</td>
<td>Brain</td>
<td>Interstitial RT → HD-MTX</td>
<td>7</td>
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<td>44/M</td>
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<td>Ocular RT → HD-MTX</td>
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<td>Brain</td>
<td>STR → MTX, Ara-C → stem cell rescue</td>
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<td>Ocular RT → HD-MTX</td>
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<td>Brain</td>
<td>GTR → HD-MTX</td>
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<tr>
<td>18</td>
<td>42/F</td>
<td>Brain</td>
<td>HD-MTX</td>
<td>6</td>
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<tr>
<td>19</td>
<td>49/M</td>
<td>Brain + ocular</td>
<td>WBRT → HD-MTX → ocular RT</td>
<td>6</td>
</tr>
<tr>
<td>20</td>
<td>59/F</td>
<td>Brain</td>
<td>HD-MTX</td>
<td>3</td>
</tr>
<tr>
<td>21</td>
<td>57/M</td>
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<tr>
<td>22</td>
<td>56/M</td>
<td>Brain</td>
<td>HD-MTX</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy; M-CHOD, methotrexate, cyclophosphamide, vincristine, Adriamycin, and dexamethasone; RT, radiation therapy; STR, subtotal resection; Ara-C, 1-β-D-arabinofuranosylcytosine; GTR, gross total resection. * HD-MTX, 3.5 g/m².

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rent Bell’s palsy (one patient). At initial diagnosis, 15 patients had disease confined to the brain only, 2 had disease confined to the vitreous, 3 had disease in the brain and vitreous, and 1 each had disease in the brain/CSF and brain/nerve (Table 1). Initial staging for all of the patients included HIV serology and lumbar puncture for cytology and flow cytometry. Computed tomography scans of the thorax, abdomen, and pelvis were obtained in selected patients.

**Initial Treatment with Methotrexate.** All of the patients received HD-MTX. Two of the 22 patients had surgical resections before chemotherapy, 5 received focal radiation before chemotherapy, and 3 received other chemotherapeutic agents besides MTX (Table 1). In these 22 patients, the median number of cycles to CR was 6 (range, 2–14), and the median time to first relapse was 24.4 months (range, 2–100 months).

**First Salvage with Methotrexate.** Recurrent disease was documented in brain in 17 patients, in vitreous in 1, in nerve in 1, in brain/ocular in 1, and in brain/CSF in 2. Nineteen patients received cycles of HD-MTX at 8 g/m², two patients at 3.5 g/m², and one patient at 3 g/m². No patients received whole-brain radiation, intrathecal chemotherapy, or other chemotherapy agents. One patient received stereotactic radiosurgery to a small residual focus of enhancing tumor. The median number of cycles to response was four (range, 1–14). CR was achieved by 16 (73%) of 22 patients, mixed response by 1 (5%) of 22 patients, partial response by 3 (14%) of 22 patients, and progressive disease by 2 (9%) of 22 patients. The overall response rate for first salvage was 91%.

**Second Salvage with Methotrexate.** Seventeen patients were at risk for recurrent disease at the completion of first salvage therapy; 7 patients relapsed and 1 was lost to follow-up. The median time to second relapse for these patients was 25.8 months [95% confidence interval (CI), 13.5–∞]. Four patients received HD-MTX for second salvage, one patient received whole-brain radiation followed by temozolomide, one patient received topotecan, and one patient refused treatment. For patients who received HD-MTX, the median number of cycles to response was 4.5 (range, 2–6). CR was achieved by two (50%) of four patients and partial response by two (50%) of four. The overall response rate for second salvage was 100%. The two patients who achieved a CR relapsed at 1.5 and 15 months. Both were treated with topotecan and whole-brain radiation for recurrent lymphoma.

**Survival.** Seven patients have died, and one has been lost to follow-up. Median survival from initial diagnosis was 91.9 months (95% CI, 47.2–∞) and from first salvage was 61.9 months (95% CI, 42.1–∞; Fig. 1).

**Univariate and Multivariate Analysis.** Results of univariate logistic regression models and analysis by Cox proportional hazards regression models revealed no variables with significant prognostic value. However, there was a trend toward significance for a relationship between increasing number of cycles during initial treatment and longer time to first relapse (hazard ratio 1.18, \( P < 0.1 \)) and between ocular involvement and longer survival after salvage (hazard ratio 3.37, \( P = 0.14 \)).

**Toxicity.** HD-MTX was well tolerated by the majority of patients. The median number of cycles for this selected cohort of patients was 25 (range, 9–58). Toxicity was primarily hematologic with four episodes of neutropenia (one grade 1, two grade 2, and one grade 4), seven episodes of thrombocytopenia (five grade 1, one grade 2, and one grade 3), two episodes of anemia (one grade 2 and one grade 1), two episodes of azotemia (one grade 1, three grade 2), four episodes of hepatotoxicity (grade 3), two episodes of allergy (grade 1), three episodes of thrombosis/embolism (two grade 3 and one grade 4), two episodes of mucositis (one grade 1 and one grade 2), two episodes of diarrhea (one grade 1 and one grade 2), and one episode of infection (grade 3). In a total of 566 cycles, there were ten episodes of grade 3 or 4 toxicity.

**DISCUSSION**

We studied the efficacy and tolerability of HD-MTX as salvage therapy for a subset of patients with relapsed CNS lymphoma who initially responded to MTX therapy. The objective response rates were 91% after first salvage (20 of 22 patients) and 100% after second salvage (4 of 4 patients). Time to relapse after first salvage with HD-MTX was similar to the time to relapse after initial treatment (25.8 months versus 24.4 months, respectively; Fig. 2). Because only patients who experienced relapse before the end of follow-up were included in this group, the median time to relapse for this sample may be an underestimate for all patients with CNS lymphoma. However, this bias should be slight because we have obtained at least 33 months of follow-up on each subject. Median survival was 61.9 months after salvage and 91.9 months after CNS diagnosis.

These findings expand on prior reports of chemotherapy for primary CNS lymphoma. In one series, 10 of 16 patients with relapsed disease after combined-modality therapy achieved a CR after salvage therapy (6). Similarly, 5 of 10 patients treated with cytarabine and etoposide in anticipation of intensive chemotherapy and stem-cell rescue achieved a CR, and 3 of 10 achieved a partial response for a response rate of 80% (14). However, not all patients treated previously with chemotherapy respond to salvage therapy. Among patients treated with MTX after blood–brain barrier disruption, those who received prior chemotherapy were substantially less likely to achieve CR than those who did not (33% versus 69%, respectively; 7). In this study, the initial response to chemotherapy was not noted. Thus, it is not known how many of these patients had progressive rather than relapsed disease.
In the present study, survival after diagnosis and survival after relapse, compared favorably with previous reports. In studies of whole-brain radiation (9), intra-arterial carboplatin (10), topotecan (11), procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNA), vincristine (PCV; ref. 12), temozolomide (13), and intensive chemotherapy followed by stem-cell rescue (14), median survival after salvage ranged from 2 to 12 months. For patients treated initially with combined-modality therapy, median survival after relapse was 27 months (6). Meta-analysis of 24 studies revealed a median survival of 14 months after salvage for patients with relapsed or refractory disease treated with a variety of regimens (8).

At the present time, there are no evidence-based guidelines to determine the optimal duration of treatment with HD-MTX. Many schedules discontinue treatment after a predetermined number of cycles or reduce the frequency of chemotherapy once maintenance is complete. Although patients who achieve a CR have no evidence of enhancing disease on magnetic resonance imaging, previous studies have documented microscopic disease in the absence of contrast-enhancing lesions (15). It is not known whether relapse is due to the failure of current maintenance schedules to achieve disease control or due to the emergence of clones resistant to MTX. Future studies of CNS lymphoma are needed to address the optimal duration of treatment with HD-MTX and to identify combined chemotherapy regimens with superior antilymphoma activity.

These data must be interpreted in the context of the study design. First, patients were highly selected to include those who achieved a complete response to initial therapy with HD-MTX. This may have led to selection of a subset of patients with tumors that were particularly sensitive to chemotherapy and, thus, were predisposed to have longer survival times. However, because 50–65% of patients with primary CNS lymphoma achieve CR with MTX monotherapy the results reported herein are potentially applicable to more than one half of all patients with primary CNS lymphoma. Second, previous studies of salvage chemotherapy often included patients with recurrent and refractory disease. Including both populations leads to lower response rates and shorter survival because patients with refractory disease do worse than those with recurrent disease.

In conclusion, salvage therapy with HD-MTX appears to be effective for patients with CNS lymphoma who relapse after initial CR to MTX. Given the low toxicity associated with HD-MTX, we believe it is reasonable to consider deferring treatment with whole-brain radiation therapy or more toxic chemotherapy regimens until these patients have been given a trial of HD-MTX. Finally, we feel that prospective studies of patients with recurrent or refractory disease are warranted, given the high rate of relapse in CNS lymphoma and the lack of established agents to treat this condition.

REFERENCES

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