Intraarterial Corticosteroid Infusion Following Radiotherapy for Primary Central Nervous System Lymphoma: Feasibility and Preliminary Result

NAOFUMI HAYABUCHI, YUKIHIRO TODA, YUTA SHIBAMOTO*, ETSUYO OGO, NORIMITSU TANAKA, KAZUYUKI KOJIMA, TOSHI ABE AND GEN SUZUKI

Department of Radiology, Kurume University School of Medicine, Kurume 830-0011 and
*Department of Therapeutic Radiology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan

Summary: To utilize the high lympholytic effect of corticosteroids with minimal systemic adverse effects, we used intraarterial corticosteroid infusion in the treatment of 8 patients with primary central nervous system lymphoma (PCNSL). One patient had recurrent PCNSL, while the other patients had primary disease. Following standard radiotherapy with or without some systemic or intrathecal chemotherapy, prednisolone (60-100 mg in total) or dexamethazone (12 mg in total) was rapidly infused through the carotid arteries in all patients and also through the left vertebral artery in 5 patients. No acute or late complications of this treatment were observed. All 8 patients achieved complete or partial response. Four patients died of the disease, while the other 4 were alive with (1 patient) or without (3 patients) disease at 8-37 months after treatment, giving a 2-year survival rate of 55%. Intraarterial administration of high-dose corticosteroids appears to be a feasible treatment modality. This method may be used in preradiotherapy setting to evaluate response of PCNSL in future studies.

Key words lymphoma, CNS, corticosteroid, radiotherapy, intraarterial infusion

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is increasing and is now one of the most important neoplasms in neurooncology. This disease has most often been treated with radiation therapy [1,2]. Although the tumor also responds to chemotherapy and favorable results have been reported for patients treated with combination of radiation and chemotherapy, the role of chemotherapy still remains controversial, due to the lack of randomized studies comparing radiation plus chemotherapy with radiation alone [3-14]. The favorable results reported for patients receiving the combination therapy may be due to the selection of patients with favorable outcome [15]. Thus, the standard treatment for PCNSL remains to be determined in future studies.

Corticosteroids are known to possess prominent oncolytic effects in PCNSL in addition to their effects to ameliorate cerebral edema. Most PCNSL diminish in size following systemic administration of corticosteroids, and even long-term control of PCNSL has been reported following steroid treatment alone [16-18]. Corticosteroids do not produce severe adverse effects which anticancer agents can produce, but long-term use of steroids can produce other complications which are quite different from those of anticancer agents. Because of the difference in toxicity, it may be useful to effectively combine steroid with radiotherapy and/or chemotherapy. To prevent recurrence of PCNSL by maximally utilizing the lympholytic effect of corticosteroids and avoiding their systemic adverse effects, we have used intraarterial topical administration of corticosteroids fol-
lowing standard radiotherapy with or without chemotherapy. In this paper, we report the results of the treatment in 8 patients.

MATERIALS AND METHODS

Between March 1996 and November 1999, 8 patients with PCNSL were treated with intraarterial corticosteroid therapy following radiotherapy. Details of the 8 patients are summarized in Table 1. The first patient had recurrent PCNSL; at the time of initial treatment, partial removal, which confirmed the diagnosis of PCNSL, followed by whole brain radiation (20 Gy) and focal boost (30 Gy) had been given. In the other 7 patients, biopsy or surgical removal was attempted in 5 patients, while 2 patients did not undergo surgical procedures, and the diagnosis of PCNSL was made clinically using the criteria similar to those proposed by other investigators [18,19]. Six of the 8 patients had multiple lesions. The World Health Organization performance status (PS) was 0 in two patients, 2 in five, and 4 in one.

The first patient with recurrent disease received focal radiation with 20 Gy. All the other patients received whole-brain radiotherapy to a dose of 30-50 Gy followed by 0-20 Gy of focal boost. The daily dose of 2 Gy was given 5 times a week. The total radiation dose was 40-60 Gy. Whole-brain radiation was given by parallel opposed fields, and focal booster doses were given by parallel opposed or lateral single field. Three of the patients received 1, 2 or 5 courses of high-dose intravenous methotrexate (3 g/m²) accompanied with leucovorin rescue (15 or 21 mg given 6 or 12 times following each methotrexate administration) before radiotherapy. The other 2 patients received intrathecal cytarabine (20 mg × 5) injection during radiation therapy. Three patients received systemic corticosteroids for 2-14 days after operation or during radiotherapy.

One to 15 days after completing radiation therapy, corticosteroids were given intraarterially by Seldinger’s method. Prednisolone was used in 7 patients, while dexamethasone was used in the other patient. Depending on the tumor location and spread, varying doses of the steroids were injected through internal carotid arteries and in 5 of the patients also through the left vertebral artery. In the first patient, 30 mg of prednisolone was given first, and then 60 mg was given again 1 month later. The total dose of prednisolone was 60 mg in the second and third patients. The fourth patient received 12 mg of dexamethasone which is equivalent to 60 mg prednisolone. The use of dexamethasone was to investigate feasibility of the drug which can be given in smaller volumes of solution. The total dose of prednisolone was increased to 75 mg in the fifth patient, and then to 100 mg in the remaining patients.

Response to treatment was evaluated by means of magnetic resonance imaging (MRI) during and immediately after radiotherapy, and after corticosteroid treatment. Also, MRI was repeated at 3-4 month intervals thereafter.

RESULTS

All patients completed the planned treatment. After corticosteroid administration, all patients were in good conditions. So far, no acute or late compli-

<table>
<thead>
<tr>
<th>Age /Sex</th>
<th>Tumor Number Size*</th>
<th>PS</th>
<th>Surgery</th>
<th>Chemotherapy</th>
<th>Radiation dose (Gy)</th>
<th>Corticosteroid dose (mg)</th>
<th>Total</th>
<th>Response</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>54/F** 1</td>
<td>30</td>
<td>2</td>
<td>None</td>
<td>None</td>
<td>20</td>
<td>30/60</td>
<td>0</td>
<td>0</td>
<td>30/60</td>
</tr>
<tr>
<td>75/M &gt;5</td>
<td>50</td>
<td>2</td>
<td>Biopsy</td>
<td>None</td>
<td>50</td>
<td>25</td>
<td>15</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>68/F 3</td>
<td>15</td>
<td>2</td>
<td>Subtotal removal</td>
<td>None</td>
<td>60</td>
<td>30</td>
<td>30</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>59/M 1</td>
<td>30</td>
<td>0</td>
<td>Subtotal removal</td>
<td>Ara-C (it)</td>
<td>50</td>
<td>5**</td>
<td>5**</td>
<td>2**</td>
<td>12</td>
</tr>
<tr>
<td>68/F &gt;5</td>
<td>25</td>
<td>2</td>
<td>Biopsy</td>
<td>MTX (iv) ×3</td>
<td>40</td>
<td>25</td>
<td>50</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>65/M 2</td>
<td>25</td>
<td>2</td>
<td>None</td>
<td>Ara-C (it)</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>60/F &gt;5</td>
<td>20</td>
<td>4</td>
<td>Biopsy</td>
<td>MTX (iv) ×5</td>
<td>50</td>
<td>30</td>
<td>50</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>46/M &gt;5</td>
<td>30</td>
<td>0</td>
<td>None</td>
<td>MTX (iv) ×2</td>
<td>50</td>
<td>50</td>
<td>30</td>
<td>20</td>
<td>100</td>
</tr>
</tbody>
</table>

*Longest diameter (mm), **Recurrent case, ***Dose of dexamethazone (prednisolone was used in the other patients)
cations of the treatment have been observed. Six of the 8 patients achieved complete response (CR), whereas two achieved partial response (PR: >50% reduction in maximum tumor area). All the 5 patients who achieved CR did so during radiotherapy. The first patient with recurrent disease had only minimal response to 20 Gy of reirradiation, but he had PR following corticosteroid infusion. Another patient with PR had achieved PR by radiation therapy, but further reduction of tumor size was not obtained following corticosteroid infusion. This patient developed local regrowth of the tumor.

Of the 6 patients with CR, two developed multiple recurrences in the brain both within and outside the boost treatment volume, and another developed recurrences in the cerebellum and eye (outside the treatment volume). Following treatment, the PS improved in 4 patients, while in the other 4 patients, PS remained at the same level. Four patients died of PCNSL at 8, 11, 23, and 26 months from the beginning of radiotherapy, while the other 4 are alive, three with no evidence of disease at 8, 26, and 37 months, and one with recurrent disease at 15 months. The median survival time for the 8 patients was 26 months, and the Kaplan-Meier survival rate was 73% at 1 year and 55% at 2 years.

DISCUSSION

It is well known that PCNSL responds to corticosteroids. This lympholytic effect of steroids is mediated by cytoplasmic steroid receptors which are translocated to the nucleus and signal apoptosis [18]. This particular response to steroids can be quite helpful in establishing clinical diagnosis of PCNSL [18,19], but obscures histological diagnosis when given before biopsy [20]. In addition to the direct effect on lymphoma cells, the "trafficking effect," that is to prevent malignant lymphoma cells from entering CNS, is also postulated [21]. If this postulation is true, steroids may play a role in preventing CNS relapse of lymphoma.

Since the effect of steroids is high, it seems reasonable to use corticosteroids in the treatment of PCNSL. Some PCNSL’s disappear following systemic administration of moderate doses of steroids, and long-term control of PCNSL by steroid treatment alone has been not infrequently reported [16-18]. Therefore, we postulated that intraarterial topical administration would produce even higher effects. Since no investigators have used such an approach, we investigated its feasibility in this study. That is, we used steroid infusion after standard treatment. We began with a single prednisolone dose of 30 mg, and finally reached the total dose of 100 mg. Fortunately, we have observed no acute or late complications so far. Thus, this approach appears to be quite feasible. There appeared to be no difference in feasibility between prednisolone and dexamethazone.

Once this approach proved to be feasible, tumor response to the treatment may be investigated in the next step. In this study, 6 of the 8 patients had achieved CR following radiotherapy, and tumor response to intraarterial corticosteroids could not be assessed in these patients. In the remaining two patients, the mass which persisted after radiation responded to the steroid treatment in one patient, but the persisting mass did not respond in the other patient and eventually showed regrowth. However, the mass persisting after radiotherapy may comprise of treatment-resistant subpopulations, so this case does not necessarily deny the antitumor effect of intraarterial steroid infusion. Although one of our patients had recurrent disease and 6 of the other 7 patients had multiple lesions, their median survival time was 26 months and their 2-year survival rate was 55%. These results compare favorably with those reported for 466 patients with PCNSL treated between 1985 and 1994 in our country (median survival: 18 months; 2-year survival: 40%) [2]. Prednisolone at the dose of 100 mg in total proved to be safe, and topical administration of such a high dose of steroid is expected to produce prominent reduction of PCNSL mass. In spite of the prominent effect of corticosteroids on PCNSL, their use in active treatment of PCNSL has been controversial [12,17,18]. One of the reasons is the adverse effect of steroids especially in long-term use. However, such a temporary use expected to produce high concentrations in tumor may be worthy of considering its incorporation into treatment regimens. The intraarterial steroid infusion can be used in combination with standard radiation and chemotherapy, and should be further evaluated in future studies. Based on these results, we have just started to use intraarterial steroid infusion before radiation therapy.

ACKNOWLEDGMENTS: This study was supported in part by the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.
REFERENCES


