Efficacy of Intravenous Cyclophosphamide Therapy for Neuromyelitis Optica Spectrum Disorder

Hiroaki Yaguchi, Ken Sakushima, Ikuko Takahashi, Hiroaki Nishimura, Moemi Yashima-Yamada, Masakazu Nakamura, Kazufumi Tsuzaka, Yasunori Maruo, Toshiyuki Takahashi, Ichiro Yabe and Hidenao Sasaki

Abstract

Objective Neuromyelitis optica (NMO) is an inflammatory disease that affects the optic nerve and spinal cord. Optic neuritis and longitudinally extensive myelitis associated with systemic autoimmune disease have been recently defined as NMO spectrum disorder (NMOSD). In this study, we report the efficacy of intravenous cyclophosphamide (IVCY) therapy for NMOSD.

Methods Four patients diagnosed with NMOSD were enrolled in this study. The expanded disability status scale (EDSS) score was used to evaluate the degree of severity. All of the patients received intravenous methylprednisolone (IVMP; 1 g/day for three days), and two patients also received plasmapheresis (PP). All of the patients were administered IVCY treatment.

Results Anti-AQP4 antibodies were present in the sera of all patients. All patients exhibited longitudinally extensive transverse myelitis (LETM). Only one patient who fulfilled the criteria for a diagnosis of NMO exhibited optic neuritis. Two patients developed relapse under treatment with low-dose prednisolone (PSL) before the administration of IVCY. The patients in this study exhibited a median improvement in the EDSS score following IVCY treatment from 8.0 to 5.75. Adverse effects were observed in only one patient.

Conclusion This study, despite its retrospective design, demonstrated the therapeutic efficacy of IVCY for NMOSD in both the acute and chronic phases of the disease and determined the IVCY dosage for Japanese women with NMOSD. Additionally, this study provided evidence that for NMOSD patients with severe disabilities, IVCY added to IVMP and PP may be a useful therapeutic modality.

Key words: neuromyelitis optica spectrum disorder, intravenous cyclophosphamide, anti-aquaporin 4 antibody, immunosuppressive therapy


Introduction

Neuromyelitis optica (NMO), an inflammatory disease that affects the optic nerve and spinal cord, is characterized by the presence of disease-specific autoantibodies, anti-aquaporin 4 (AQP4) antibodies, in the serum. Wingerchuk et al. defined optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease as a type of NMO spectrum disorder (NMOSD) (1). Intravenous cyclophosphamide (IVCY) is an immunosuppressant that is frequently used for the treatment of patients with neuropsychiatric systemic lupus erythematosus (NPSLE) (2) and central nervous system symptoms associated with Sjögren’s syndrome (SS) (3). In addition, the European Federation of Neurological Societies (EFNS) recommends IVCY treatment as second-line therapy for patients with NMO, especially in cases where NMO is associated with systemic lupus.
Patients (Table 1)

Four patients diagnosed with NMOSD (1, 4) were enrolled in this study and treated with IVCY at the departments of neurology of two general hospitals (Hakodate Municipal Hospital and Kushiro Rosai Hospital) and one university hospital (Hokkaido University Hospital) between January 2007 and May 2011. The presence of serum anti-AQP4 antibodies was confirmed in all patients by the Department of Multiple Sclerosis Therapeutics, Tohoku University Graduate School of Medicine (5). Rheumatologists applied the classification criteria for SLE (6) and SS (7) to all of the patients. We reviewed the medical records and collected data retrospectively regarding the course of NMOSD, including diagnostic imaging results, laboratory findings, patient treatment regimens and outcomes. The expanded disability status scale (EDSS) score (8) was used to evaluate the degree of severity at the time of recurrence and at the point of the last IVCY initiation. The Institutional Review Board of Hokkaido University Hospital approved this clinical study.

Materials and Methods

Patients (Table 1)

Table 1. Patient Profiles

<table>
<thead>
<tr>
<th>Patient</th>
<th>onset age</th>
<th>sex</th>
<th>follow up (year)</th>
<th>HT</th>
<th>BS</th>
<th>LETM</th>
<th>ON</th>
<th>other</th>
<th>neurological symptom</th>
<th>auto-antibody</th>
<th>AQP4 OCB</th>
<th>SLE</th>
<th>SS</th>
<th>APS</th>
<th>NMO revised criteria</th>
<th>NMOSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>F</td>
<td>4.8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
<td>arthritis/lymphadenitis</td>
<td>ANA/SSB</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>F</td>
<td>3.9</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
<td>nephritis/thrombosis</td>
<td>ANA/dsDNA/LAC</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>F</td>
<td>2.2</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
<td>neuropathy</td>
<td>ANA/dsDNA/aCL</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>F</td>
<td>4.2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>


Table 2. Treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Times</th>
<th>Months</th>
<th>Cy mg/mm²</th>
<th>PSL (mg/day) before IVCY</th>
<th>PSL (mg/day) after IVCY</th>
<th>AQP4 OCB</th>
<th>SLE</th>
<th>SS</th>
<th>APS</th>
<th>plasmapheresis</th>
<th>side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>18</td>
<td>500</td>
<td>0</td>
<td>11</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>8</td>
<td>500</td>
<td>5</td>
<td>10</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>12</td>
<td>468</td>
<td>0</td>
<td>5</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>12</td>
<td>468</td>
<td>20</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>UTI+sepsis</td>
<td>-</td>
</tr>
</tbody>
</table>

Cy: cyclophosphamide, PSL: prednisolone, IVCY: intravenous cyclophosphamide, UTI: urinary tract infection

Figure 1. Therapeutic regimens of all of the patients. Triangle: intravenous cyclophosphamide (IVCY), square: plasmapheresis, white circle: non-neurological symptom, black circle: neurological symptom, black line: low dose PSL. In Patients 1 and 2, systemic symptoms, except for neurological symptoms, were present. In two patients (Patients 2 and 4), low-dose PSL did not prevent recurrence.

The demographics of the four patients are summarized in Tables 1 and 2 and in Fig. 1. All patients were women, and the average age at onset of NMOSD symptoms was 37.0 (SD, 14.6) years. The mean follow-up period after the initiation of IVCY treatment was 3.78 (SD, 0.97) years (range, 2.2-4.8 years). Anti-AQP4 antibodies were present in the sera of all patients. All patients exhibited longitudinally extensive transverse myelitis (LETM), as indicated in Fig. 2 and Table 1. Only one patient who fulfilled the criteria for the NMO diagnosis exhibited optic neuritis (9). One patient was diagnosed with SLE and two patients were diagnosed with SS. One patient was diagnosed with anti-phospholipid
antibody syndrome (APS). In two patients, the symptoms of NMO were preceded by other systemic symptoms (nephropathy, arthritis, lymphadenitis and thrombosis), while one patient exhibited neuropathy. Two patients experienced relapse while under treatment with low-dose prednisolone (PSL) at a mean dose of 12.5 mg/day, before the administration of IVCY. The dosage of IVCY administered to the patients averaged 500 mg/m², except for Patient 1, who required a higher dosage (774 mg/m²) (Table 2). For all patients other than Patient 1, the mean frequency of administration was 10 doses of IVCY per month (Table 2). This was similar to previously published methodology (2). Patient 1 was administered azathioprine (AZP) after IVCY treatment.

The patients in this study showed a median improvement in the EDSS score following IVCY treatment from 8.0 to 5.75 (Fig. 3). Although a higher IVCY dose was required for Patient 1, treatment with an adequate dose of IVCY prevented symptom recurrence in three patients. Moreover, in all patients, IVCY treatment improved the neurological symptoms during the subacute phase of the disease. This was especially noted in Patient 4, who showed marked improvement in neurological symptoms after treatment during the acute phase. Adverse effects (sepsis) were observed in only one patient.

**Representative case (Patient 3): EDSS score improvement after IVCY treatment in the acute phase**

Patient 3 was a 34-year-old woman with a history of several episodes of optic neuritis and positive results for autologous antibodies. The patient had developed paraplegia, urine ischuria, sensory disturbances and hypoalgesia and was unable to maintain a sitting position. Although two previous courses of IVMP followed by oral PSL and PP therapy resulted in mild improvement of her neurological symptoms, she was unable to walk on her own. Her EDSS score improved slightly from 8.5 to 7.5. Therefore, IVCY was administered to reduce her neurological symptoms and prevent recurrence. The IVCY therapy improved the results of the manual muscle test (MMT) of the lower extremities from 3/5 to 5/5, and the patient was able to stand and walk on her own. One year later, her EDSS score had improved from 7.5 to 3.5 (Fig. 3).

After IVCY treatment, she did not show any recurrence of neurological symptoms with the administration of 7.5 mg/day of PSL. However, reducing the PSL dose to 5 mg/day for approximately one year resulted in the recurrence of optic neuritis.

**Discussion**

In this study, we summarized our experience with IVCY treatment for NMO patients. Our results confirm and extend the findings of other investigations. Specifically, IVCY therapy may be effective for NMO patients in both the acute and chronic phases of the disease.

The identification of anti-AQP4 antibodies as a disease-specific marker has greatly expanded the scope of NMO diagnosis. Wingerchuk et al. defined optic neuritis or LETM associated with systemic autoimmune disease as an NMO (1). Thus far, several studies have suggested that immunosuppressive therapies (low-dose PSL, AZP, mitoxantrone, rituximab, oral CY and mycophenolate mofetil [MMF]) prevent NMO relapse (4). IVCY has also been recommended as a second-line therapy in NMO patients, especially in cases where NMO is associated with SLE or SS (4). In addition, the efficacy of IVCY for the treatment of the neurological symptoms of SLE and SS has already been reported (2, 3). However, the results of these studies cannot be directly extrapolated to NMO patients because anti-AQP4 antibodies were not measured and patients who did not show the neurological symptoms of NMO were...
included (2). Therefore, further investigation of the efficacy of IVCY treatment for NMOSD is necessary. To our knowledge, only five cases of IVCY treatment for NMOSD have been reported (10). In four of these cases, the patients tested positive for anti-AQP4 antibodies. Furthermore, in one case, low-dose PSL, MMF, tacrolimus, daily oral CY and rituximab were unable to prevent relapse, while IVCY treatment successfully prevented relapse (10). Additionally, Petelin Gadze et al. reported that IVCY administration resulted in good clinical improvement during the subacute phase in a patient with NMO (11).

Our results suggest that IVCY is effective in reducing neurological symptoms during the acute phase (Fig. 3). Although IVMP and PP might have achieved a delayed therapeutic effect, in one NMO patient (Patient 3) who exhibited only a mild recovery following PP therapy, IVCY treatment resulted in a marked improvement in neurological symptoms in the acute phase. A maintenance dosage of 500 mg/m² every month over a period of 6-12 months seems to be effective for Japanese NMOSD patients. However, one patient (Patient 1) was resistant to IVCY therapy and required a dosage of up to 774 mg/m². Moreover, these dosages are consistent with the regimens for IVCY recommended by the EFNS, which range from 7 to 25 mg/kg per month over a period of six months (4).

Additionally, our results also suggest that IVCY was effective in preventing recurrence in three patients (Patients 1, 2 and 4) with NMOSD and is therefore effective for the treatment of patients who experience relapse. In Patient 4, although low-dose PSL did not prevent recurrence, the addition of IVCY treatment to low-dose PSL could have prevented the recurrence (Fig. 1 and Table 2). On the other hand, in Patient 3, the administration of PSL at a dose of 5 mg/day after IVCY treatment did not prevent recurrence. Therefore, the dose of PSL must be carefully tapered following IVCY treatment.

In conclusion, despite the lack of a unified protocol for IVCY and its retrospective design, this study demonstrated the therapeutic efficacy of IVCY for NMOSD in both the acute and chronic phases of the disease and determined the IVCY dosage for Japanese women with NMOSD. Additionally, this study provided evidence that, for NMOSD patients with severe disabilities, IVCY in addition to IVMP and PP may be a useful therapeutic modality.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
We are grateful for the assistance of Dr. Tatsuya Atsumi, Dr. Shinsuke Yasuda, Dr. Nobutaka Ogura and Dr. Shin Furukawa for the diagnosis of SLE and SS.

References