The Long-Term Prognosis of Lupus Nephritis Patients Treated with Intravenous Cyclophosphamide

Naomi Matsuyama¹, Shinji Morimoto¹, Yoshiaki Tokano², Hirofumi Amano², Kazuhisa Nozawa², Hiroshi Isonuma¹, Hiroshi Hashimoto² and Yoshinari Takasaki²

Abstract

Objective Patients with lupus nephritis receiving intravenous cyclophosphamide (IVCY) therapy were divided into groups according to their clinical course, and the long-term prognosis was evaluated.

Patients and Methods A total of 67 patients with lupus nephritis were enrolled and divided as follows into the following groups: Group A: patients with fresh nephritis, Group B: patients with relapse nephritis, Group C: patients with nephritis as a transition of the main clinical manifestation. IVCY (500 mg or 750 mg) was administered every month, and continued for two to more than six months.

Results The rate of remission was 78%; group A revealed a significantly higher rate of remission compared with the other groups. Although long-term remission was revealed in most patients, some patients in Group B demonstrated a decreased rate of remission. Concerning the total dose administered, there was no relation to prognosis; a high dose was not required, especially for patients in Group A. On the other hand, the combination of steroid pulse therapy with IVCY revealed a moderate relation to the increased rate of remission in Group A. However, this combination therapy was not related to the maintenance of remission. There was no adverse effect at late onset.

Conclusion The long-term prognosis of IVCY differed according to the patient’s clinical course, and the result differed from those reported in other countries. Therefore, we should consider the clinical course and race specificity for the Japanese subject.

Key words: SLE, lupus nephritis, IVCY, steroid pulse, prognosis

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Introduction

Intravenous cyclophosphamide (IVCY) therapy has been accepted internationally for the treatment of lupus nephritis, ever since it was first reported about twenty years ago (1) and further studies (2-5) have revealed its efficacy. Most studies concerned with this therapy have been conducted as randomized controlled trials (RCT) at the National Institutes of Health (NIH) (1-5). The results of the first RCT revealed the efficacy of this therapy (1, 2), and the second RCT revealed the efficacy of long-term therapy (3). Further, the results of the third RCT revealed the efficacy of the combination therapy with steroid pulse therapy (4, 5). IVCY studies have mainly been conducted using American subjects consisting of Caucasians and Afro-Americans. However, since patients with severe nephritis and obesity were frequently observed among the American subjects who were mainly enrolled in these studies, the result is not necessarily adequate for Japanese subjects. Indeed, in European subjects, the Euro Lupus Nephritis Trial (ELNT) showed that even low dose IVCY therapy is capable of achieving sufficient efficacy (6). Thus, we postulate that IVCY therapy has some risk for adverse effects, therefore we can not simply apply the results of the NIH study to Japanese subjects. However, there have been only a few studies concerning the efficacy of IVCY in Japanese patients. Our previous study first demonstrated the efficacy in Japanese patients, and these results

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were related to the lymphocyte marker (7). However, this study only revealed the efficacy of short-term prognosis, and included heterogeneous patients of various clinical courses, combinations of other therapies and doses. Therefore, the relation to these factors needs to be investigated. Further, the follow-up for patients with insufficient or poor efficacy should also be investigated.

Here, we demonstrated the long-term prognosis of 67 Japanese patients with lupus nephritis receiving IVCY, and the factors related to its efficacy were investigated retrospectively.

### Patients and Methods

#### Patients

A total of 67 patients with lupus nephritis were enrolled in this study. All patients were treated at Juntendo Hospital from 1989 to 2001, and fulfilled the criteria of ACR (8). In 36 cases, renal biopsy was performed, and these cases were divided according to the classification of the World Health Organization (WHO): type II, 3 cases; type III, 6 cases; type IV, 22 cases; type V, 4 cases; type VI, 1 case. Most patients were unable to achieve the remission state with steroid therapy administered for one month. Steroid therapy was described as 40-60 mg/day of prednisolone or semipulse therapy (methylprednisolone 500 mg/day three days). Remission was defined by the criteria described in our previous study (9), complete or incomplete remission in this criteria was defined as “remission” and “worsen” in the previous study was defined as “relapse” in the present study.

Some patients were unable to receive high-dose steroid therapy due to adverse effects, and were immediately treated with IVCY.

The enrolled patients had various clinical courses; 17 patients were treated for fresh nephritis, and 33 patients were treated for relapse nephritis. The 17 patients were treated for nephritis as the transition of the main clinical manifestation. Nephritis as the transition of the main clinical manifestation was defined in our previous study (10), as patients with no nephritis at the time of the initial diagnosis and who had nephritis during the disease course. These initial main manifestations were defined in our previous study (10). The initial manifestations of these patients were as follows: thrombocytopenia (4 cases), autoimmune hemolytic anemia (AIHA) (2 cases), leukopenia (2 cases), serositis (2 cases), pneumonia (1 case), rash (4 cases), arthritis (1 case) and rheumatoid arthritis (1 case).

#### Methods

Patients were administered 500 or 750 mg IVCY every month, and continued from twice to more than six times. However, patients with less than 30 ml/min of creatinine clearance were administered 100 or 200 mg IVCY. The number of administrations varied depending on the status of remission or the social condition, mainly related to the co-operation of the individual patient. As for the results, 18 patients received a total dose of more than 2 g, while 49 patients received less than 2 g. The former patient’s treatments were generally terminated within 4 treatments, since complete remission was achieved. Some patients were excluded since it was not possible to follow these patients as outpatients.

Concerning combination therapy, 35 patients received 20-50 mg/day of prednisolone, 24 patients received semipulse therapy and 5 patients received plasma exchange therapy. As for the plasma exchange therapy, the double filtration or immune absorption method was used. Four patients received other immunosuppressive agents for maintenance during remission and the dose of steroid was tapered. Two patients received cyclosporin A, and 2 patients received azathioprine or mizoribine.

Since IVCY therapy is not recognized as an official therapy, informed consent was obtained at the beginning of therapy.

#### Statistical analysis

The difference of the mean value was estimated with the non-parametric test, and the difference in ratio was estimated with the \( \chi^2 \) test. The long-term prognosis in the rate of remission or without double creatinine was estimated by the Kaplan-Meier Life-table method, and differences among groups were compared using the Log Rank test.

#### Result

**The efficacy of IVCY**

First, patients were divided according to the clinical course as previously described; Group A: patients with fresh nephritis, Group B: patients with relapse nephritis, Group C: patients with nephritis as the transition of main clinical manifestation, and the efficacy was determined using the criteria previously described (9). Of the patients enrolled in this study (67 cases), 46 patients (78%) had remission, while the condition of 13 cases was unchanged (Table 1). A total of 8 patients were excluded from the study due to adverse effects (leukopenia: 2 cases, liver dysfunction: 1 case, SIADH: 1 case, hypogammaglobulinemia: 1 case), early death by pneumocystis pneumonia (1 case) and non-compliance to therapy (2 cases). Most of these problems were noted early in the patient's disease course, and there was no episode recorded during the late stage of the disease course. Among these groups, 93.8% (15 cases) of Group A had achieved remission, while 74.1% (20 cases) of Group B and 68.8% (11 cases) of Group C were in remission. Thus, the rate of remission in Group A was significantly higher than Group B or C (p<0.05). The number of drop-out cases was high in Group B (6 cases).

**Long-term prognosis of patients with remission**

Next, the long-term prognosis of patients with remission

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Table 1. Efficacy of ICVY after Six Months of Administration

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<tr>
<th>Number</th>
<th>Remission †</th>
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<tr>
<td>Total</td>
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Null hypothesis: Group A = Group B = Group C (p=0.00579)

† "Remission" includes complete remission, incomplete remission as defined in reference 9.
‡ Due to side effects (leukopenia: 2 cases, liver dysfunction: 1 case, SIADH: 1 case, hypogammaglobulinemia: 1 case), death due to pneumocystis pneumonia (1 case), and non-compliance to therapy (2 cases).
※ Percentage indicated by the number of patients/number of "remission" + "no change" cases
† p < 0.05 versus Group B or C calculated by χ² test

Figure 1. Long-term prognosis of patients with remission with ICVY therapy. Group A includes patients with fresh patients with fresh nephritis, Group B includes patients with relapse nephritis and Group C includes patients with nephritis as the transition of the main clinical manifestation. The remission rate of Group B was significantly decreased as compared with Group A or C (Log Rank test: p<0.05).

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Figure 2. The relation between remission and renal prognosis. The rate of without double creatinine levels in patients with relapse after remission (Group(2)) or without remission (Group(3)) significantly decreased as compared with patients with remission (Group(1)) (Log Rank test p<0.01).

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patients with relapse after remission and 3) patients without remission. When the number of patients without double creatinine levels were examined, the number was significantly decreased in patients with relapse after remission [ Group (2) ] or without remission [ Group (3) ] (p<0.01), as shown in Fig. 2. And, when the survival rate was examined, the number of patients without remission was significantly decreased (p<0.05) (data not shown). Thus, the prolongation of remission is closely related to the frequency of renal failure and survival.
The relation between the course of remission and clinical profile were examined. As shown in Table 2, all patients with relapse after remission [Group (2)] were identified in Group B, and the duration of the disease of these patients was significantly longer than the other groups [Group (2)] (p<0.05). Pathological evaluation revealed that all patients with WHO type II or III had long-term remission, while some patients with WHO type IV had no remission or relapse (data not shown). Thus, patients with a long duration of the disease state or severe pathological findings had a poor prognosis.

**The relation to total dose or combination therapy**

Next, the relation to total dose administered was investigated, and the patients were divided into two groups as follows: low dose group (received less than 2 g as total dose) and high dose group (received more than 2 g). As to the results, there was no difference in the efficacy (data not shown). As shown in Fig. 3, there was also no difference in the rate of long-term remission between the two groups. Indeed, those patients with fresh nephritis resulted in remission they did not have a relapse at any dose of IVCY.

Then, the relation to combination therapy was investigated among Groups A, B and C. The relation between the combination of steroid pulse therapy and efficacy revealed that patients receiving steroid pulse therapy had higher efficacy (with pulse: 81.8%, without: 69%) and this tendency was stronger in Group A (with pulse: 100%, without pulse: 66.7%). Further, when the relation of long-term prognosis was examined in patients revealing efficacy, the remission rate in patients receiving steroid pulse therapy tended to be greater (Fig. 4). However, there was no significant differ-
ence.

Further, multi-quantitative analysis concerning the total dose of IVCY and the combination of steroid pulse or plasma exchange was performed by the Cox hazard model. The results were similar to those in Fig. 3 or 4 (data not shown).

**The disease course of patients without remission**

A total of 12 patients without remission were examined: 4 patients received azathioprine (AZ), and 3 patients attained remission, 1 patient without remission with AZ received oral cyclophosphamide, another patient received mizoribine, and was unable to attain remission. She received hemodialysis (HD), but died due to uremia. Of the 7 patients who did not receive any intensive therapy or without remission, 1 patient received HD, but died due to infection, and 3 patients who had not received HD died due to brain hemorrhage, CNS lupus and thrombosis of the sagittal sinus.

**Discussion**

In this study, we investigated the long-term prognosis of IVCY in Japanese patients and the relation to various factors. In the results some interesting findings were revealed.

First, we demonstrated the fact that the efficacy was related to the clinical course. In brief, patients with fresh nephritis had good efficacy, while patients with relapse nephritis or patients with nephritis as the transition of main clinical manifestation had the worst efficacy. However, in previous studies, the patients were not divided according to these factors. Originally, in our study, the patients with relapse nephritis or nephritis as the transition of main clinical manifestation had the worst efficacy. However, in previous studies, the patients were not divided according to these factors. Originally, in our study, the patients with relapse nephritis or nephritis as the transition of main clinical manifestation had the worst efficacy as compared with those with fresh nephritis (11). Although good efficacy of IVCY is expected in patients with any of these courses (11, 12), we should consider the difference in efficacy among the courses of nephritis. On the other hand, none of the patients with fresh nephritis had a relapse, while some patients with relapse nephritis had recurrent episodes of nephritis. Thus, the frequency of relapse was also related to the course of nephritis. However, patients with nephritis as the transition of the main clinical manifestation did not have relapse, although the efficacy of this group was not favorable. This result was related to the fact that some of the patients received immunosuppressive agents for maintenance of remission, and it is possible that there was some form of bias. It is interesting why these differences were identified. One possibility is that these patients with relapse nephritis or the nephritis as the transition of the main clinical manifestation had a high chronidity index. It is generally speculated that IVCY is unable to improve the chronidity index. Certainly, some patients with relapse nephritis or nephritis as the transition of the main clinical manifestation had a high chronidity index, and the fact that patients with a long duration of disease had a poor prognosis may support this possibility. However, we were unable to evaluate the relation between the efficacy and the chronidity index, since the number of cases was very small. And, we cannot neglect the relation to the pathological type, since all patients with WHO type II, III had good response and some patients with WHO type IV or V had a poor prognosis. Further, although we were unable to evaluate the relation, in the future we should consider the relation to new classification of ISN (2003). Another possibility is the difference in the immunological status. Our previous study revealed that the efficacy of IVCY is related to the activation of T cells, and our recent study (13) revealed the difference in Th1/Th2 balance between fresh onset and relapse cases. Certainly, some patients with relapse had a high ratio of activated T cells and Th2 cells. However, there was no significance, and it is suggested that various causes may be related to the difference in efficacy.

In the present study, we revealed new findings concerning the total dose administered. As previously described, the total dose of IVCY was mainly reported by the NIH group (3) or ELNT (6). However, there are no established data for the Japanese subjects. In the present study, two groups were formed with 2 g total dose as the cut-off point, and the number of patients was bisected. In the results, there was no significant difference in efficacy or relapse, and this result may suggest that the IVCY therapy in Japan is administered at a lower dose than in foreign countries. Unfortunately, although the number of patients in our study was limited and we were unable to conduct sufficient analysis, we believe that there are no relations to the total dose administered that may be common in any course of nephritis. However, although some patients with a high chronidity index were administered a high dose, most patients had no insufficient efficacy (data not shown). Therefore, we also should consider the relation between this result concerning dose and the chronidity index. On the other hand, in this study, we noticed that the rate of remission generally decreased after two years, especially in patients with relapse nephritis. Even though some patients were able to maintain long-term remission, we cannot neglect the possibility that the total dose administered was low even in the higher dose group (total dose of more than 2 g). We should further investigate patients receiving much higher doses similar to the NIH group protocol especially in the patient group with relapse nephritis. Presently, we are investigating these patients, and would like to compare the result with the present study in the future. Although most of our patients did not receive immunosuppressive agents for maintenance therapy, these patients did not have relapse. While the recent studies stress the importance of this maintenance therapy (14), in the present study, we were unable to establish the necessity of this therapy especially among the fresh nephritis patients. However, we cannot neglect the fact that some patients with nephritis as the transition of the main clinical manifestation maintained their state of remission with immunosuppressive agents, as previously described. Thus, we should clarify the issue concerned with considering the total dose administered...
and the maintenance therapy.

Further, we investigated the relation between combination therapy and the prognosis. In the results, the patients with fresh nephritis receiving steroid pulse therapy had a better efficacy. However, there was no significant difference in long-term remission. The NIH group (4, 5) clearly demonstrated that the prognosis of patients receiving steroid pulse therapy was significantly better. It is certain when concerned with efficacy that our result may support their study. Our previous study (7) demonstrated that B cells are influenced by IVCY therapy, while steroid pulse therapy influences T cells. Furthermore, this study also revealed that patients with a high ratio of activated T cells had a low efficacy of IVCY therapy. This difference of the effect between steroid and IVCY may be related to the better efficacy of combination therapy of steroid pulse therapy and IVCY. However, we previously described that the difference is unclear in the long-term remission cases, and we should evaluate this result carefully. On the other hand, in our study, we can not neglect that five patients receiving PEX had a better prognosis (data not shown). Most of these patients had persistently low complement levels and high titers of anti-double strand DNA antibody, and PEX therapy was selected and performed. Our recent study revealed that PEX in lupus nephritis had a similar efficacy to IVCY (15). Therefore, the combination of PEX is expected to induce better efficacy.

Lastly, we demonstrated the prognosis of patients without favorable outcomes with IVCY. These patients were generally miserable, and unable to obtain the sufficient state of remission with the initial steroid therapy at disease onset. Therefore, intensive therapy including IVCY should be recommended in patients unable to attain sufficient remission by steroid therapy, since there was no adverse effect in long-term administration of IVCY (ovarian failure, malignancy) in the present study. However, since most young patients were Conscious about the adverse effect, they did not consent to intensive therapy, and this coincides with the findings of an American report (16). In our previous study (12) and the study of the NIH group (1, 2), patients with severe nephritis receiving only steroid never related to poor prognosis. In the present study, we also revealed that some patients without efficacy of IVCY had remission with azathioprine. Therefore, we speculated that the indication of IVCY for the initial therapy should be carefully evaluated, although we generally recommend this therapy to patients with relapse nephritis.

This study is our first report concerning the long-term prognosis of IVCY therapy in Japanese patients, and the preliminary results of this study are presented. We are currently conducting further studies, and different findings may be presented in the future after the completion of the ongoing study.

References