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# V.　研究成果の刊行物・別刷

（主なもの）

# Long-term responses and outcomes following immunosuppressive therapy in large granular lymphocyte leukemia-associated pure red cell aplasia: a Nationwide Cohort Study in Japan for the PRCA Collaborative Study Group

Naohito Fujishima,[1] Ken-ichi Sawada,[1] Makoto Hirokawa,[1] Kazuo Oshimi,[2] Koichi Sugimoto,[2] Akira Matsuda,[3] Masanao Teramura,[4] Masamitsu Karasawa,[5] Ayako Arai,[6] Yuji Yonemura,[7] Shinji Nakao,[8] Akio Urabe,[9] Mitsuhiro Omine,[10] and Keiya Ozawa[11]

[1]Division of Hematology and Oncology, Department of Medicine, Akita University School of Medicine, Akita, Akita; [2]Division of Hematology, Juntendo University School of Medicine, Bunkyo-ku, Tokyo; [3]Department of Hematology, Saitama International Medical Center, Saitama Medical University, Hidaka, Saitama; [4]Department of Hematology, Tokyo Women's Medical University, Shinjuku-ku, Tokyo; [5]Blood Transfusion Service, Gunma University Hospital, Maebashi, Gunma; [6]Department of Hematology, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo; [7]Blood Transfusion Service, Kumamoto University School of Medicine, Kumamoto, Kumamoto; [8]Cellular Transplantation Biology, Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa; [9]Division of Hematology, NTT Kanto Medical Center, Shinagawa, Tokyo; [10]Internal Medicine, Showa University Fujigaoka Hospital, Yokohama, Kanagawa, and [11]Division of Hematology, Department of Medicine, Jichi Medical University, Shimotsuke, Tochigi, Japan

## ABSTRACT

Large granular lymphocyte leukemia-associated pure red cell aplasia accounts for a significant portion of secondary pure red cell aplasia cases. However, because of its rarity, long-term responses and relapse rates after immunosuppressive therapy are largely unknown. We conducted a nationwide survey in Japan and collected 185 evaluable patients. Fourteen patients with large granular lymphocyte leukemia-associated pure red cell aplasia were evaluated. Cyclophosphamide, cyclosporine A and prednisolone produced remissions in 6/8, 1/4 and 0/2 patients respectively. Seven and 5 patients were maintained on cyclophosphamide or cyclosporine A respectively. Two patients relapsed after stopping cyclophosphamide, and 2 patients relapsed during maintenance therapy with cyclosporine A. The median relapse-free survival in the cyclophosphamide - and the cyclosporine A groups was 53 and 123 months respectively. Large granular lymphocyte leukemia-associated pure red cell aplasia showed a good response to either cyclophosphamide or cyclosporine A. Most patients continued to receive maintenance therapy and it remains uncertain whether cyclophosphamide or cyclosporine A can induce a maintenance-free hematologic response in large granular lymphocyte leukemia-associated pure red cell aplasia.

Key words: pure red cell aplasia, large granular lymphocyte leukemia, cyclophosphamide, cyclosporine.

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## Introduction

Large granular lymphocyte (LGL) leukemia is the most common underlying disease of secondary pure red cell aplasia (PRCA) in a single institutional study from the United States, and the second most common cause in Japan.[1-3] LGL leukemia is also referred to as granular lymphocyte-proliferative disorders (GLPD) or lymphoproliferative disease of granular lymphocytes.[1,2,4-6] LGL leukemia is a heterogeneous disorder characterized by a persistent increase in the number of peripheral blood LGLs, and the majority of patients have a clonal rearrangement of T-cell receptors.[4,6,7] Clonal disorders of LGLs may arise from natural killer cells, and may be indolent or behave as an aggressive disease. Neutropenia is the

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*Correspondence: Naohito Fujishima, M.D., Division of Hematology and Oncology, Department of Medicine, Akita University School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan. E-mail: naofuji@doc.med.akita-u.ac.jp*

most frequent cytopenia in T-cell LGL leukemia, and anemia is also caused by various mechanisms in 48% of the patients.[8,9]

LGL leukemia-associated PRCA has been primarily treated with chemotherapy, such as oral cyclophosphamide (CY) with or without prednisolone (PSL), cyclosporine A (CsA), or methotrexate.[5,9,10,11] The combination of CY and PSL is associated with a longer duration of response than PSL alone.[1,10,12] The overall response to initial CY therapy has been reported to be 66-100%[5,11] and the median duration of response is 32 months.[11] However, optimal management of LGL leukemia-associated PRCA and long-term outcome after immunosuppressive therapy are largely unknown because of the rarity of this disorder.

The efficacy and long-term outcome after immunosuppressive therapy for secondary PRCA might differ according to the underlying diseases. We, therefore, conducted a nationwide survey to investigate the current status of immunosuppressive therapy for acquired chronic PRCA based on a relatively large patient cohort in Japan. This report is a summary focusing on immunosuppressive therapy for LGL leukemia-associated PRCA.

## Design and Methods

### Data collection of the data and patients' characteristics

As described elsewhere,[3,13] the questionnaires were sent to 109 hematology departments in Japan, and a total of 185 evaluable patients were collected from 45 institutions. Seventy-three patients were classified as having idiopathic PRCA and 112 patients had secondary PRCA.[3] Diagnosis of LGL leukemia was based on the presence of a persistent (>6 months) increase in the number of peripheral blood LGL (>500/mL), since the normal range for peripheral blood LGL counts is 223±99/μL[14] and clonal disease has been documented in 8% of patients when absolute LGL counts are in a range from 600 to 1,000/mL.[8] A 6-month follow-up criterion was not applied when clonality was established.[4] Fourteen patients (7.6%) were found to have both LGL leukemia and PRCA (Table 1). Rearrangement of T-cell receptor (TCR) was examined in 11/14 patients. In case 12, the diagnosis of LGL-leukemia was established on morphological criteria. Case 13 has been previously reported.[15] A unique patient number was given at each participating institution to protect individual information. This study was approved by the institutional review board, and performed according to the declaration of Helsinki and the ethical guidelines for epidemiological research of the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare of Japan.

### Definition of response and data analysis

Definition of response and data analysis has been described elsewhere.[3,13] Relapse was defined as the reappearance of transfusion requirement. In some analyses, the patients were classified according to the agent used for maintenance therapy such as the CY group or the CsA group regardless of the agents used for successful remission induction. The agents for remission induction and salvage therapy were defined as those used initially and those used either sequentially or in a later combination respectively. Survival was estimated by the Kaplan-Meier method and statistical difference was calculated by the log-rank test. Endpoints of this study were the response rate, the relapse-free survival (RFS) and overall survival (OS).

## Results and Discussion

### Response to the first remission induction therapy

The initial treatment for these patients included CY (n=8), CsA (n=4), and PSL (n=2). For one patient (case 2) who had been given PSL for rheumatoid arthritis before the onset of PRCA, CsA was determined as the initial agent for PRCA. CY achieved CR and PR in 2 and

**Table 1. Characteristics of large granular lymphocyte leukemia-associated pure red cell aplasia.**

| Case | Observation period | Age/ Sex | WBC (/μL) | Lym (%) | LGL (/μL) | Hb (g/dL) | CD3 (%) | CD4/8 | CD56 (%) | TCR rearrangement |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2001-2007 | 85/F | 7,460 | 68 | 4,849 | 7.2 | 98.4 | 0.12 | 0.6 | + |
| 2 | 2005-2006[a] | 84/F | 5,670 | 18 | 964 | 6.1 | 97.7 | 0.20 | 1.2 | + |
| 3 | 1999-2007 | 56/M | 3,470 | 55 | 1,562 | 6.6 | 96 | 0.36 | 5.9 | + |
| 4 | 2004-2007 | 69/M | 5,500 | 81 | 4,345 | 5.5 | 88 | 1.00 | 11.5 | + |
| 5 | 1996-2007 | 58/M | 7,300 | 78 | 3,176 | 7.2 | 99 | 0.20 | 2.9 | + |
| 6 | 2004-2007 | 62/M | 12,880 | 79 | NA | 7.6 | NA | 0.12 | NA | + |
| 7 | 1999-2007 | 71/F | 2,990 | 52 | NA | 5.1 | NA | 0.20 | NA | NA |
| 8 | 1994-2007 | 45/M | 6,500 | 48 | 1,092 | 5.7 | 97 | 0.12 | 3 | + |
| 9 | 1996-2007 | 44/F | 3,400 | 54 | 993 | 3.4 | 97 | 0.33 | 4 | + |
| 10 | 2005-2007 | 65/F | 3,200 | 73 | NA | 6.3 | 96.9 | 0.55 | 0.7 | + |
| 11 | 2002-2007 | 64/F | 11,000 | 50 | NA | 9.8 | NA | NA | NA | + |
| 12 | 1993-2007 | 52/M | 3,200 | 27 | NA | 5.5 | 92.3 | 0.66 | 18 | - |
| 13 | 1992-1999[b] | 55/M | 7,400 | 80 | 2,960 | 3.4 | 97 | 0.17 | NA | + |
| 14 | 1996-2006[a] | 76/M | 6,500 | 55 | 2,730 | 4.5 | 94 | NA | 0.6 | + |

*NA: not available; F: female; M: male; BW: body weight; WBC: white blood cells; Lym: lymphocytes; LGL: large granular lymphocytes; Hb: hemoglobin; TCR: T-cell receptor; [a]: follow-up-end; [b]: dead.*

4 patients respectively. Response rate was 75%. The median initial dose of CY for the responding patients (n=6) was 100 mg with a range of 50-100 mg. Two non-responding patients were also given 100 mg of CY. When the patients who responded to initial CY therapy were evaluated, the time for transfusion-independence from the start of therapy was 29±45 days (range 0-92 days). Four patients achieved transfusion-independence within two weeks and 5 patients within three months. One patient achieved remission later than six months from the start of CY therapy. The median duration of CY therapy (including remission induction and maintenance therapy) was 24 months with a range of 10-124 months.

CsA achieved a response in 1/4 (25%) patients. The initial dose of CsA for the responding patient (case 8) was 200 mg (3.7 mg/kg), and he achieved transfusion-independence within two weeks. Although one patient was given 450 mg (8.8 mg/kg) of CsA for 49 days, he did not respond (case 6). PSL did not produce any clinical response (n=2). In these patients, the initial doses of PSL were 0.9 mg/kg (case 9) and 0.4 mg/kg (case 13). Two out of 14 patients (14%) responded neither to CY nor CsA. There was no significant difference in the response to the first remission induction therapy between CY and CsA by the $^2$ test.

### Salvage therapy for non-responders to the first remission induction therapy

Seven patients failed to respond to remission induction therapy. In 2 patients who failed to respond to the initial CY therapy for 77 (case 10) and 182 days (case 14), one patient (case 10) responded to CsA. Another patient (case 14) did not respond to the sequential salvage therapies including CsA, azathioprine and methotrexate. All 3 patients who failed to respond to the initial CsA therapy for 36 (case 2), 49 (case 6) and 176 days (case 7) responded to CY. In 2 patients who failed to respond to the initial PSL therapy, one patient (case 9) responded to CsA. Although the other patient (case 13) partially responded to anti-thymocyte globulin (ATG) after the sequential administration of CsA and CY, he died of pneumonia.

### Duration of response to immunosuppressive therapy

We classified the patients with LGL leukemia-associated PRCA according to the agent used for maintenance therapy as the CY group (n=7, cases 1-7) and the Csa group (n=5, cases 8-12) (Figure 1). Four out of 12 (33%) patients relapsed and they were 2 patients (cases 1 and 3) of the CY group and 2 patients (cases 9 and 12) of the CsA group. Estimated median duration of the RFS in the CY group (53 months) was shorter than that

| Case | BW (kg) | a) Agents in order or combination | b) Initial Dose (mg) | | | | c) Tf-dep. Period (days) | d) RFS1 | e) Maintenance (mg) | f) Relapse | g) RFS2 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Cyclophosphamide-group (n=7)* | | | | | | | | | | | |
| 1 | 50 | CY | 50 | | | | 0 | 9.7 | Off | Yes | 21.0 |
| 2 | 47 | CsA/CY | 140 | 50 | | | 113 | 4.0 | Off | No | 11.1+ |
| 3 | 64 | CY | 100 | | | | 80 | 14.5 | Off | Yes | 38.5 |
| 4 | NE | CY | 50 | | | | 0 | 16.1 | Off | No | 6.1+ |
| 5 | NE | CY-MTX | 100 | 2.5 | | | 0 | 31.4 | Off | No | 0.0+ |
| 6 | 51 | CsA/CY | 450 | 50 | | | 196 | 22.7+ | CY 25 | No | |
| 7 | 38 | CsA/CY | 200 | 50 | | | 20 | 33.0+ | CY 50 | No | |
| *Cyclosporine-group (n=5)* | | | | | | | | | | | |
| 8 | 54 | CsA | 200 | | | | 0 | 119.8+ | CsA 100 | No | |
| 9 | 66 | PSL/CsA | 60 | 200 | | | 115 | 77.1 | CsA 100 | Yes | |
| 10 | NE | CY/CsA | 100 | 200 | | | 92 | 14.7+ | CsA 50 | No | |
| 11 | 66 | CY/CsA | 100 | 150 | | | 0 | 60.3+ | CsA 150 | No | |
| 12 | NE | CY-AZP/CsA | 100 | 50 | 200 | | 941 | 122.8 | CsA 150 | Yes | |
| *Non-responders* | | | | | | | | | | | |
| 13 | 48 | PSL-CsA/CY/ATG | 20 | 350 | 100 | ND | 175 | 4.0 | PSL 10 | Yes | |
| 14 | 41 | CY/CsA/AZP/MTX | 100 | 300 | 50 | ND | 3318+ | NE | Off | NE | NE |

CR PR NR

Figure 1. Response to immunosuppressive therapy and relapse of anemia in large granular lymphocyte-associated pure red cell aplasia. NE:not evaluable, a) Agents are listed in order(/); in sequential administration,(-); in combination later on,b) The initial dose and response to the agents; the order of agents corresponds to that shown in column, c) Transfusion-dependent period (days) after the initiation of remission induction therapy, d) RFS1; relapse-free survival (months) estimated as transfusion-free survival is shown as the period before the discontinuation of maintenance therapy, e) Off; tapered off) Relapse was defined as reappearance of transfusion requirement, g) RFS2; RFS after the discontinuation of maintenance therapy.

| Case | BW (kg) | a) Agents in order or combination | b) Initial Dose (mg) | | | | c) Tf-dep. Period (days) | d) RFS1 | e) Maintenance (mg) | f) Relapse | g) RFS2 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 50 | CY | 25 | | | | 0 | 21.0 | Off | Yes | 18.0 |
| 3 | 64 | CY/CsA | 50 | 200 | | | 253 | 8.8 | Off | Yes | 15.0 |
| 9 | 66 | CsA-CY | 200 | 50 | | | 20 | 47.8+ | CsA 200 | No | |
| 12 | NE | CY/MTX/CsA | 50 | 2.5 | 150 | | 47 | 4.7+ | CsA 125 | No | |

CR PR NR

Figure 2. Immunosuppressive therapy for relapsing patients. See Figure 1 for abbreviations.

of the CsA-group (123 months) with statistical significance ($p$=0.0423). Maintenance therapy was discontinued in 5 patients in the CY-group, and 2 patients relapsed at 21 and 39 months after the discontinuation of CY. Three patients have still maintained remission after the discontinuation of CY, but the RFS after discontinuation of CY was only 0, 6 and 11 months (RFS2 in Figure 1). Although all 5 patients in the CsA group were still on maintenance therapy, 2 patients relapsed.

### Immunosuppressive therapy for relapsing patients

Two patients in the CY group, who relapsed after the discontinuation of maintenance CY therapy, again responded to CY and were maintained in remission with CY for 21 (case 1) and nine months (case 3) (Figure 2). However, they relapsed again at 18 (case 1) and 15 months (case 3) after the discontinuation of CY, but later responded to CsA (*data not shown*). Two patients in the CsA-group relapsed during maintenance CsA therapy. Trough levels of CsA in case 9 and 12 when their anemia relapsed were 93.0 ng/mL and unknown respectively. One patient (case 9) partially responded to CsA and completely responded to the latter in combination with CY. The other patient (case 12) did not respond to the sequential administration of CY and methotrexate, but again responded to CsA (Figure 2).

### Mortality and overall survival

One patient (case 13) died of infection following ATG therapy at 85 months after the onset of PRCA. The estimated median overall survival time has not yet been reached with the median observation period of 87 months (from 19 to 170 months) and the estimated 10-year overall survival (OS) after the onset of PRCA was 86%.

Despite a relatively small number of patients, we have demonstrated that the overall response rate to initial CY therapy is 75% in LGL leukemia-associated PRCA. CY seemed to have a better activity in remission induction of LGL leukemia-associated PRCA than CsA, but this was not statistically significant. In contrast, CsA has been shown to be the most effective agent for idiopathic and thymoma-associated PRCA[3,13] so the efficacy of these agents may differ depending upon the sub-types of PRCA.

Although remission induction can be achieved in the majority of patients with LGL leukemia-associated PRCA, a further problem is concern over how many patients treated with CY or CsA achieve a sustained remission and how many relapse, and whether or not there is need for maintenance treatment. We have reported that the discontinuation of maintenance CsA therapy is strongly correlated with relapse in idiopathic PRCA patients,[3] and that thymoma-associated PRCA may also be CsA-dependent.[13] In the present study, there were 3 patients who maintained remission after the discontinuation of CY; however, each relapse-free period after the discontinuation was still only 0, 6 and 11 months. Considering that a relapse can occur even 39 months after the discontinuation of CY, these observation periods may be insufficient to conclude that LGL-leukemia can be cured by CY.

There is general agreement that alkylating agents are the most powerful medications for treating autoimmune disease.[16] Although CY seems to be a key drug for remission induction of LGL leukemia-associated PRCA, the duration of the maintenance therapy is one of the major concerns considering the late toxicity of CY.[12] The risk of toxicity from alkylating agents is related to the cumulative dose of the medication and the duration of therapy.[17-19] Bladder cancer and myelodysplastic syndrome are the most common malignancies associated with daily CY therapy.[17,21] Therefore, strategies that reduce the duration of exposure can minimize the long-term risks. In a series of 7 patients with T-cell-LGL leukemia-associated PRCA, all patients were successfully treated with oral CY monotherapy.[5] Therapeutic responses began after eight weeks, and clinical CRs were obtained after six months. Clinical remission was associated with the disappearance of TCR rearrangement, which suggests that the disappearance of TCR rearrangement may be an indicator for the discontinuation of CY.

No secondary malignancy has been reported up to now in the present patient cohort. The median duration of maintenance CY therapy was 16 months with a range of 4–33 months, suggesting some difficulty in stopping CY while trying to maintain remissions. Interestingly, 2 patients who responded to CY could be maintained with CsA for 60 and 123 months (cases 11 and 12 respectively). We speculate that CY is of limited value as a maintenance agent due to its late toxicity, which may be the reason why the actual median RFS in the CY group (53 months) was shorter than that of the CsA group (123 months).

It remains uncertain whether immunosuppressive agents can induce maintenance-free hematologic response, as is the case with idiopathic[3] or thymoma-associated PRCA.[13] Considering the recurrent nature of LGL leukemia-associated PRCA, CsA may be an effective alternative to prevent relapse of anemia following successful remission induction with CY. The median OS of all patients has not yet been reached with a median observation period of 90 months and an estimated 10-year OS of 86%, which suggests that LGL leukemia-associated PRCA has a relatively good prognosis.

In conclusion, we have demonstrated for the first time that most patients with LGL-associated PRCA are still receiving maintenance therapy and may be CY/CsA-dependent. Effective and less toxic maintenance therapy to prevent relapse of anemia needs to be established.

## Appendix

*The following institutions participated in the Collaborative Study Group: Aichi Medical School, Akita University, Asahikawa Medical School, Chiba University, Dokkyo Medical School, Ehime University, Fujita Health University, Fukui University, Fukui National Hospital, Fukuoka University, Fukushima Medical University, Gifu University, Gunma University, Hamamatsu Medical School, Hirosaki*