Long-term response and outcome following immunosuppressive therapy in thymoma-associated pure red cell aplasia: a nationwide cohort study in Japan by the PRCA collaborative study group

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ABSTRACT

Background
Thymoma-associated pure red cell aplasia (PRCA) accounts for a significant proportion of cases of secondary PRCA and immunosuppressive therapy has been reported to be useful in this condition. However, because of its rarity, the long-term response and relapse rates after immunosuppressive therapy are largely unknown, and optimal management of this disorder remains unclear. The aim of this study was to collect more information on the outcome of patients with thymoma-associated PRCA.

Design and Methods
We conducted a nationwide survey in Japan. From a total of 185 patients, comprising 73 with idiopathic and 112 with secondary PRCA, 41 patients with thymoma were evaluated for this report. End-points of this study were the response rate, duration of the response after immunosuppressive therapy and overall survival.

Results
Surgical removal of thymoma was reported in 36 patients, 16 of whom developed PRCA at a median of 80 months post-thymectomy. First remission induction therapy was effective in 19 of 20 patients treated with cyclosporine, 6 of 13 patients treated with corticosteroids and 1 of 1 treated with cyclophosphamide. No cyclosporine-responders relapsed within a median observation period of 18 months (range; 1 to 118 months). Relapse of anemia was observed in three corticosteroid-responders who did not receive additional cyclosporine. Only two patients were in remission after stopping therapy for 19 and 67 months. The estimated median overall survival time of all patients was 142 months.

Conclusions
Thymoma-associated PRCA showed an excellent response to cyclosporine and cyclosporine-containing regimens were effective in preventing relapse of anemia. It does, however, remain uncertain whether cyclosporine can induce a maintenance-free hematologic response.

Key words: pure red cell aplasia, thymoma, cyclosporine.

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Introduction

Acquired pure red cell aplasia (PRCA) is an anemic condition characterized by the absence of reticulocytes in blood and the absence of erythroid precursors in the bone marrow.[1-4] Other hematopoietic cell lineages are present with no evident morphological abnormalities. Secondary PRCA is associated with various underlying diseases including lymphoproliferative disorders, thymoma, solid tumors, autoimmune diseases, drugs and viral infections.[1,2] The association of PRCA with thymoma was first described in 1928 by Matras and Priesel,[1] and thymoma-associated PRCA accounts for a significant proportion of the secondary cases.[5,6] Thymoma-associated PRCA is generally thought to be an organ-specific autoimmune disease as well as an idiopathic form, and immunosuppressive therapy, including corticosteroids, cyclophosphamide and cyclosporine, has been reported to be useful.[5,7,8,9] Thompson *et al*. recently reported their 50-year single institution experience with 13 patients with thymoma-associated PRCA,[10] and showed that surgical resection of the thymoma was insufficient to induce normalization of erythropoiesis, and that anti-thymocyte globulin was an effective adjuvant treatment but associated with high treatment-related morbidity due to frequent infectious complications. However, the optimal management of thymoma-associated PRCA and the long-term outcome after immunosuppressive therapy remain unclear because of the rarity of this disorder.

The efficacy and long-term outcome after immunosuppressive therapy for secondary PRCA could differ according to the underlying diseases. To date, the overall long-term response and relapse rates after immunosuppressive therapy in acquired PRCA are largely unknown. We, therefore, conducted a nationwide survey to investigate the current status of immunosuppressive therapy for acquired chronic PRCA based on a relatively large cohort of patients in Japan. This report is a summary focusing on immunosuppressive therapy for thymoma-associated PRCA.

Design and Methods

Data collection and patients' characteristics

The first questionnaires were sent to 109 hematology departments in Japan to estimate the number of patients aged 15 and above who had been newly diagnosed as having acquired PRCA between 1990 and 2006. Patients with human parvovirus B19 infection-associated PRCA were excluded. Eligible patients were limited to those who had been diagnosed during this period in order to minimize the effect of transfusion-associated hepatitis C virus infection. Overall, 273 patients were enrolled from 45 institutions. Secondary questionnaires were then sent to these institutions to collect data regarding underlying diseases, laboratory findings including peripheral blood cell counts and leukocyte differentials, results of bone marrow examination, immunological and cytogenetic parameters, efficacy of immunosuppressive therapy and outcome. Morphological diagnosis of bone marrow was done by hematologists at each institution. Of the 185 patients identified, 73 patients were classified as having idiopathic PRCA and 112 as having secondary PRCA.

The classification of PRCA was based on the criteria proposed by the Hematopoietic Organs Research Committee of the Ministry of Health, Labor and Welfare of Japan in 2005.[11] This classification was fundamentally based on the criteria proposed by Dessypris and Lipton.[2] Forty-two patients had both thymoma and PRCA. One patient who had undergone autologous hematopoietic stem cell transplantation for recurrent malignant thymoma before the onset of PRCA was excluded from this study, so 41 patients were finally selected for analysis of thymoma-associated PRCA. Personal identifying information was protected by giving each data set a unique patient number at each participating institution. 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, Labor and Welfare of Japan.

The age of the patients at the onset of PRCA ranged from 27 to 82 years (median age, 66 years) and there was a 3:4 male to female ratio of cases. Autoimmune diseases and malignancies were complications in 11 and five patients, respectively (Table 1). Thymoma histology was varied with one case of type A, nine type AB, three type B1, and four type B2 cases according to the WHO classification of histological typing of tumors of the thymus.[12] Hyperplasia was reported in one case, and histological subtypes could not be determined in 23 cases. The hemoglobin concentration ranged from 2.7 to 10.9 g/dL with a median of 5.8 g/dL.

Table 1. Co-morbidity in patients with thymoma-associated PRCA (n=41).

Underlying diseases	*Number of patients*
Autoimmune disease	11
Myasthenia gravis	6
Systemic lupus erythematosus	1
Mixed connective tissue disease	1
Dermatomyositis	1
Polyneuropathy	1
Autoimmune hemolytic anemia	1
Malignancy	5
Myelodysplastic syndrome	1
Stomach	1
Breast	1
Thyroid	1
Bladder	1

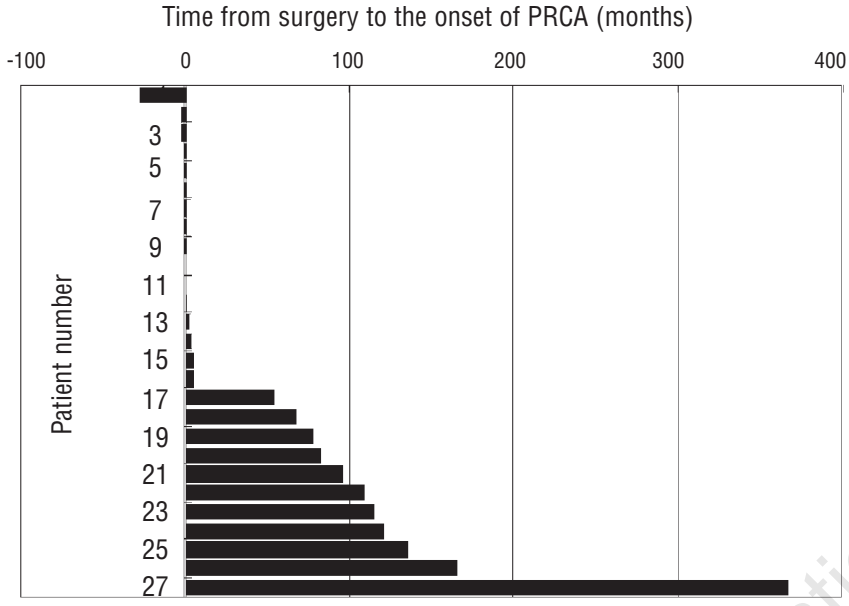

Figure 1. Chronological sequence of surgical removal of the thymoma and the onset of PRCA. The time when each patient underwent surgery is located at point 0 on the x-axis. Data were available for 27 patients.

Table 2. The first remission induction therapy for thymoma-associated PRCA.

	N.	*CR*	*PR*	*NR*	*Response rate*
Cyclosporine	20	16	3	1	19/20 (95%)
Corticosteroids	13	5	1	7	6/13 (46%)
Cyclophosphamide	1	1			1/1 (100%)
Anabolic steroid	1			1	0/1 (0%)
None	6				

Definition of the responses and data analysis

Complete remission (CR), partial remission (PR) and no response (NR) were defined as the achievement of normal hemoglobin levels without transfusion, the presence of anemia but without transfusion dependence, and continued dependence on transfusions, respectively. The date of remission was defined as that of the final transfusion after the initiation of remission induction therapy. The minimum period required for evaluation of response to agents was set at 2 weeks; therefore, agents added within 2 weeks were included into a simultaneous combination with the preceding agents. In some analyses, the patients were classified according to the agent used for maintenance therapy, e.g. a cyclosporine group and a non-cyclosporine group, regardless of the agents used successfully to induce remission. The agents for remission induction and salvage therapy were divided into those used initially and those used either sequentially or in a later combination, respectively. The agent for maintenance therapy was defined as that used or tapered off after successful induction of remission. Relapse was defined as the reappearance of transfusion requirement. Survival was estimated using the Kaplan-Meier method and the significance of differences was calculated by the log-rank test. The end-points of this study were the response rate, duration of the response to immunosuppressive therapy and overall survival. Secondary endpoints included the time from surgical removal of the thymoma to the onset of PRCA.

Results

Surgical removal of the thymoma

Thymomectomy was performed in 36 patients, while four patients did not undergo surgery. Data on surgery were not available for one patient. The chronological sequence of thymoma removal and the onset of PRCA could be analyzed in 27 of the 36 patients: the thymoma was resected before the onset of PRCA in 16 patients, with the anemia developing a median of 80 months after surgery (range; 1 to 366 months) (Figure 1). Eleven patients underwent surgery after the diagnosis of PRCA. In the remaining nine patients, the time of surgery was unknown.

Five patients underwent surgery without any adjuvant therapy: two of these patients had no response, while the clinical response was unknown in the other three patients.

Rate of response to the first remission induction therapy

The initial treatment for these patients included cyclosporine (n=20), corticosteroids (n=13), cyclophosphamide (n=1) and an anabolic steroid (n=1) Six patients did not receive any medication (Table 2).

Cyclosporine produced CR or PR in 19/20 patients

Table 3. Effective salvage therapy for patients who failed to respond to the first remission induction therapy.

UPN	Remission induction therapy			Salvage therapy	
	Initial agent	Response (@ days)	Discontinuation	Agent	Response
125	Methyl-PSL* PSL	NR (105)	Yes No	CsA	CR
37	PSL	NR (250)	No	CsA	PR
99	FK506* PSL	NR (75)	Yes No	CsA	CR
44	Anabolic steroid	NR (125)	Yes	CsA	PR

PSL: prednisolone; CsA: cyclosporine A; CR: complete remission; PR: partial remission; NR: no response.

(95%). The patients who responded to cyclosporine had histological type A, type AB and type B1 thymoma. The median initial dose of cyclosporine for the responding patients was 4.6 mg/kg body weight (b.w.) with a range from 2.0 to 6.3 mg/kg b.w. The non-responding patient was given 3.9 mg/kg b.w. of cyclosporine. All evaluable cyclosporine-responders (n=15) became independent of blood transfusions within 2 weeks after starting treatment (*data not shown*).

Corticosteroids produced CR or PR in 6/13 patients (46%). The median initial doses of corticosteroids for the responding and non-responding patients were 1.0 mg/kg b.w. (range, 0.3 to 1.1 mg/kg) and 0.8 mg/kg (range, 0.3 to 1.2 mg/kg), respectively. Three evaluable corticosteroid-responders became independent of transfusions 0, 9 and 135 days after starting therapy. Three of six corticosteroid-responders were given additional cyclosporine and were maintained in CR (n=2) and PR (n=1).

Cyclophosphamide was administered to one patient who had a complete response. The time to response from the start of therapy was unknown. The one patient treated with an anabolic steroid did not achieve a clinical response.

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

The patient who failed to respond to initial cyclosporine therapy did not receive any other immunosuppressive treatment, and continued to receive transfusions. Of the seven patients who failed to respond to the initial corticosteroid therapy, five were then treated with cyclosporine therapy, resulting in a response in three of these patients. These three patients were continuously given corticosteroids after starting cyclosporine (Table 3). One patient who failed to respond to the initial treatment with an anabolic steroid was given cyclosporine and achieved a PR.

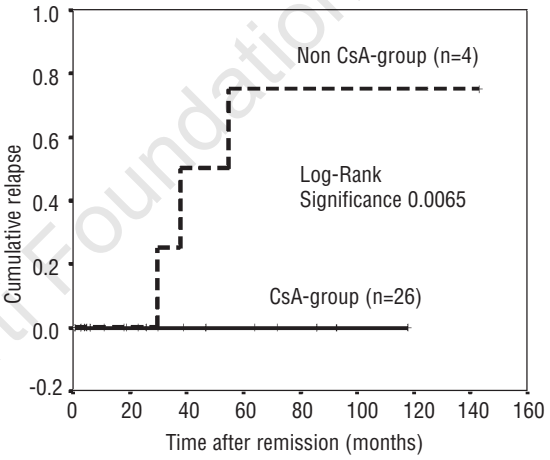

Figure 2. Cumulative incidence of relapse following immunosuppressive therapy in thymoma-associated PRCA. Relapse was defined as the reappearance of transfusion requirement. The cyclosporine-group (CsA-group) consisted of the following patients; 19 patients who had responded to the initial cyclosporine therapy, 3 patients who responded to corticosteroid therapy followed by additional cyclosporine, and four patients who received cyclosporine as salvage therapy. There was a significant difference in the duration of the response between the two groups based on the log-rank test ($p<0.01$).

Duration of the response and overall survival

There were no relapses among the 19 patients who responded to the first remission induction therapy with cyclosporine (median observation period of 18 months; range, 1 to 118 months). Three corticosteroid-responders were given additional cyclosporine and were maintained in continuous remission. In contrast, relapse of anemia was observed in three other corticosteroid-responders who did not receive cyclosporine. The patient who responded to cyclophosphamide has remained in CR for 19 months after stopping treatment. There were no relapses among the four patients who failed to respond to the first remission induction therapy but responded to salvage treatment with cyclosporine (Table 3).

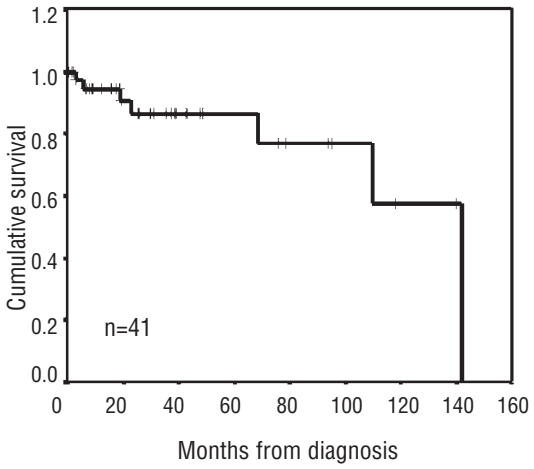

Figure 3. Overall survival of all patients with thymoma-associated PRCA (n=41).

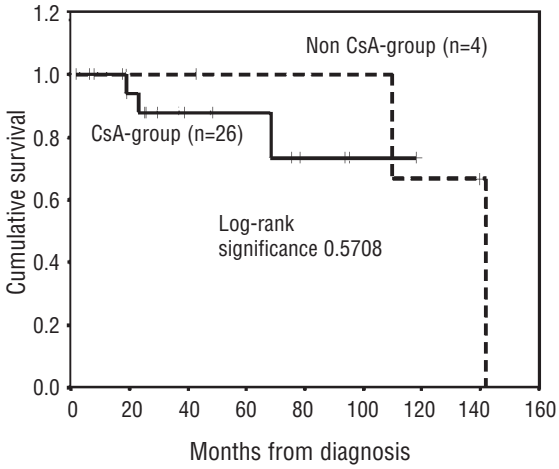

Figure 4. Comparison of the overall survival between the cyclosporine-group and the non-cyclosporine-group.

The patients were classified into a cyclosporine group and a non-cyclosporine group according to the agent used for maintenance therapy, regardless of the drugs that had successfully induced remission. Comparing the duration of response, there was a significant difference between the two groups (Figure 2; p=0.0065). However, 22 out of the 26 patients in the cyclosporine group were still on maintenance cyclosporine therapy (median dose of cyclosporine, 2.5 mg/kg; range, 0.5 to 5.0 mg/kg; median duration of maintenance, 18 months). Three patients who had received corticosteroids and additional cyclosporine were continuously given corticosteroids after cessation of the cyclosporine, and remained in remission (duration of cyclosporine maintenance; 7, 10 and 16 months). Only two patients (one treated with cyclosporine and one with cyclophosphamide) were alive in CR after stopping all immunosuppressive therapy (19 and 67 months).

The estimated median overall survival of all patients with thymoma-associated PRCA was 142 months (Figure 3). Overall survival did not differ substantially between the cyclosporine group and non-cyclosporine-group (Figure 4, p=0.5708). Seven patients died: the causes of death were infection in four patients and malignant thymoma in one patient. Two patients treated with cyclosporine and one with corticosteroids died of infection during hematologic remission. In two patients, the cause of death could not be identified.

Discussion

Cyclosporine produced excellent responses in patients with thymoma-associated PRCA, although most patients continued to receive cyclosporine for maintenance therapy. This suggests that most physicians consider it difficult to discontinue maintenance cyclosporine therapy. Sawada *et al*. reported that discontinuation of maintenance cyclosporine therapy was strongly correlated with relapse in patients with idiopathic PRCA.[11] As for idiopathic PRCA, remissions from thymoma-associated PRCA may also be cyclosporine-dependent. If this is true, other therapeutic modalities may be required to cure thymoma-associated PRCA.

Continuous immunosuppression is associated with an increased risk of infection and malignancy.[13,14] Among the patients with a good clinical response to immunosuppressive therapy, four patients died and in three of these, death was associated with infection during remission of anemia. The age of patients who died of infection ranged from 48 to 61 years, suggesting that infection may not necessarily be a complication of elderly patients only and that adequate prevention and treatment of infection are requisites for the successful management of patients with thymoma-associated PRCA. Although we have not yet had a report of malignancy secondary to immunosuppressive therapy in the present cohort of patients, continuous careful follow-up is required for patients receiving long-term cyclosporine therapy.

Limited information suggests that patients with thymoma-associated PRCA have a poor prognosis.[15-17] The median age of the patients in the present cohort was 66 years, and the estimated overall survival time was 12 years. Life expectancies of average 65-year-old Japanese males and females are 18 and 23 years, respectively (*http://www.mhlw.go.jp/english/index.html*), thus suggesting that the life expectancy of thymoma-associated PRCA patients is shorter than that of the

average Japanese population. It should be noted that the outcome of thymoma-associated PRCA can be affected by the histology of the thymoma.

Surgery is performed in thymoma-associated PRCA with the expectation of an improvement of anemia, and thymomectomy has been reported to result in occasional improvement of PRCA.[1] Surgical resection of the thymoma has been recommended as the initial treatment of thymoma-associated PRCA, with an expected hematologic response rate of 25-30%.[18] In our cohort, five patients received surgical care alone after the diagnosis of anemia; two patients did not show any improvement of anemia, and the clinical response to removal of the thymoma could not be evaluated in the other three patients. Thompson *et al.* recently reported that surgical resection of thymoma was insufficient for normalization of erythropoiesis in all 13 patients so treated, but immunosuppressive therapy was effective as an adjuvant treatment.[10] As described earlier, many patients developed PRCA at long intervals after removal of the thymoma, raising the question as to whether thymoma indeed plays a role in the pathogenesis of anemia. Masuda *et al.* reported the case of a patient with thymoma-associated PRCA and clonal T-cell expansions in both the thymoma and circulating blood,[19] whereas we have recently described a patient with a clonal T-cell expansions in the blood but not in the thymoma.[20] Thus, the role of thymoma in providing an environment for clonal expansions of pathogenic T cells may be different among individuals.

In conclusion, we have deermined, for the first time, the long-term response and outcome of patients with thymoma-associated PRCA receiving immunosuppressive therapy. Although cyclosporine produces excellent responses in thymoma-associated PRCA, it can lead to infectious complications and careful follow-up is recommended. It remains unknown whether cyclosporine can induce a maintenance-free hematologic response. Although adequate prevention of infection will be essential, the efficacy of newly developed agents such as campath-1 may be evaluated in patients refractory to cyclosporine treatment.[21]

Authorship and Disclosures

MH performed the research, collected and analyzed the data, and wrote the paper; K-iS designed the study, analyzed the data and revised the manuscript; NF collected and analyzed the data. SN, AU, KD, SF, YY, FK, MO and KO collected and analyzed the data, and revised the manuscript. All authors are responsible for the scientific content of this manuscript and approved the manuscript to be published. The authors reported no potential conflict of interest.

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 University, Hiroshima University, Hokkaido University, Hyogo Medical University, Iwate Medical School, Jichi Medical School, Jikei University, Juntendo University, Kagawa Childrens' Hospital, Kagawa University, Kagoshima University, Kanazawa University, Kanazawa Medical School, Kansai Medical University, Kawasaki Medical School, Keio University, Kinki University, Kitazato University, Kobe University, Kochi University, Kumamoto University, Kurume University, Kyoto Prefectural University, Kyoto University, Kumamoto Medical Center, Kyushu University, Mie University, Nagasaki University, Nagoya City University, Nagoya Medical Center, Nagoya University, Nara Medical University, National Cancer Center, National Institute of Infectious Diseases, Niigata University, Nishi Sapporo National Hospital, Nippon Medical School, Nippon University, NTT Kanto Medical Center, Oita University, Okayama Medical Center, Okayama University, Osaka City University, Osaka Medical School, Osaka National Hospital, Osaka University, Ryukyu University, Saga University, Saitama Medical School, Sapporo Medical School, Sendai Medical Center, Shimane University, Shinsyu University, Showa University, St. Marianna University, Teikyo University, Toho University, Tohoku University, Tokai University, Tokushima University, Tottori University, Tokyo Medical Center, Tokyo Medical School, Tokyo Medical and Dental University, Tokyo University, Tokyo Women's Medical School, Tsukuba University, University of Occupational and Environmental Health, Wakayama Medical University, Waseda University, Yamagata University, Yamaguchi University, Yamanashi University, Yokohama City University.

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