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Induced complete remission faster in adult patients with acquired pure red cell aplasia by combining cyclosporine A with corticosteroids

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Abstract

To evaluate whether the adult patients with acquired pure red cell aplasia (PRCA) could benefit more from cyclosporine A (CsA) combined with corticosteroids (CS) than CsA or CS alone.

Seventy-three patients were evaluated in 2 institutions (6 patients lost to follow-up).

The induction therapy included CsA (n = 21), CS (n = 21), or CsA combined with CS (n = 31), and remission was achieved in 16/21 (76.2%), 10/21 (47.6%), and 21/31 (71.0%) patients, respectively. Higher complete remission (CR) rate was achieved in CsA combined with CS group than in CS group (61.3% vs 19.0%, $P = .003$). Patients achieved CR faster in CsA combined with CS group than in CS group or CsA group (median time, 1 month vs 2 month vs 3 month, $P = .010$). By multivariate analysis, CsA combined with CS therapy and primary PRCA were the influence factors for CR rate. Twenty-seven patients relapsed due to discontinuation or tapering therapy, and 19 patients regained response by increasing the dose of original regimens or changing to other immunosuppressive therapy. Complete remission to induction therapy was a correlative factor for death ($P = .035$).

CsA combined with CS produced faster and higher CR rate in treating adult patients with PRCA than did CsA or CS alone.

Abbreviations: ATG = anti-thymocyte globulin, CMV = cytomegalovirus, CR = complete remission, CS = corticosteroids, CsA = cyclosporine A, EBV = Epstein–Barr virus, Hb = hemoglobin, HBV = hepatitis B virus, HIV = human immunodeficiency virus, IGH = immunoglobulin heavy, KIRs = killer cell inhibitory receptors, LGL = large granular lymphocyte, NR = no response, PR = partial remission, PRCA = pure red cell aplasia, TCR = T cell receptor.

Keywords: corticosteroids, cyclosporine A, efficacy, impact factors, pure red cell aplasia

1. Introduction

Adult acquired pure red cell aplasia (PRCA) is a rare syndrome characterized by a severe normocytic anemia, reticulocytopenia, and absence of erythroblasts from an otherwise normal bone marrow.[1] Remissions have been achieved by immunosuppressive treatment with corticosteroids (CS), cyclophosphamide, cyclosporine A (CsA), anti-thymocyte globulin (ATG), anti-CD20 monoclonal antibody rituximab, and the anti-CD52 monoclonal antibody alemtuzumab (campath-1H).[2–8] Means reported that CsA had better effect on PRCA than did CS based on literature review.[9] However, a Japanese nationwide survey of PRCA cases indicated that CsA and CS produced similar remissions in primary PRCA patients.[10] To understand the real efficacies of CsA and CS treatment in China, and whether CsA combined with CS could benefit the patients, we report the clinical outcomes of 79 adult patients with acquired PRCA in Chinese Eastern Collaboration Group of Anemia.

2. Methods

2.1. Patients

Clinical characteristics and the treatment outcomes of 79 patients with acquired PRCA (aged 18 years and over) were collected from October 2009 to March 2018 in the First Affiliated Hospital of Jilin University and the First Affiliated Hospital of Nanjing Medical University/Jiangsu Province Hospital. Inpatient cases were collected by electronic health records, and the treatment and schedules of outpatient cases were collected by clinic. Evaluations for the possible causes of PRCA include a previous history of drug use and toxins or infections including cytomegalovirus (CMV),

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Epstein–Barr virus (EBV), human immunodeficiency virus (HIV), and hepatitis B virus (HBV); liver and kidney functions; immunological examination including auto-antibodies and subset of T cells; bone marrow examination including morphology and biopsy; cytogenetics (chromosome analysis); rearrangement of T cell receptor (TCR) analysis; immunoglobulin heavy (IGH) chain gene rearrangement; and detection of STAT3 mutation. Utilization of TCRVβ repertoire and killer cell inhibitory receptors (KIRs) in peripheral blood were evaluated by flow cytometry, and computed tomography was used to rule out the presence of thymoma and neoplasms. Diagnosis of PRCA was determined when isolated anemia, in the presence of normal white cell and platelet counts, was associated with a marrow of normal cellularity in which there was an almost complete absence of erythroblasts but normal myeloid cells and megakaryocytes.[1]

2.2. Regimens

Patients received immunosuppressive treatment consisting of CsA and/or CS initially. All patients had induction therapy and responsive patients maintained the induction therapy which produced remission. Regimens in this study include CsA alone, CS alone, and CsA combined with CS. CS or CsA alone means the regimen only contain one drug. CsA combined with CS means CS and CsA were started at the same time. CsA started at a dose of 5 mg/kg/d, and the level of concentration in peripheral blood was adjusted to 150–200 ng/mL according to the side effects. CsA had been continued to ensure continuous improvement in blood counts. CS started at a dose of prednisone 0.5–1 mg/kg/d, maintained for at least 3 months. A slow tapering of the medicine (25 mg CsA every 2–3 months, 5 mg prednisone every 2 weeks) started after at least a further 12 months of therapy, to reduce the risk of later relapse. Complete remission (CR), partial remission (PR), and no response were defined as the achievement of normal hemoglobin (Hb) levels without transfusion, the presence of anemia without transfusion dependency, and persistent dependence on transfusions, respectively. Salvage therapy would be started for nonresponders after 3 months' initial induction therapy. Refractory PRCA was defined as failure to more than 2 regimens. Relapse was defined as new requirement for transfusion.[7,10] This retrospective study was conducted in compliance with good clinical practice and the ethical principles of the Declaration of Helsinki.

2.3. Statistical analyses

Statistical analyses were performed using SPSS 20. Differences among variables were evaluated by the chi-square test (or Fisher exact test for cell frequencies < 5) and t test for continuous variables. Correlation analyses of relevant factors and efficacy were analyzed by the log-rank test. The overall survival was estimated by the Kaplan–Meier method and Cox regression. $P < .05$ was considered statistically significant.

3. Results

3.1. Clinical, physiological, and laboratory findings of PRCA at initial diagnosis

These patients included 33 male and 46 female whose ages at diagnosis ranged from 26 to 84 years (median age, 55.5 years). Seventy-three patients were evaluated in 2 institutions (6 patients lost follow-up: 5 primary, 1 secondary). The Hb levels of the patients at diagnosis ranged from 1.9 to 10.0 g/dL (median Hb level = 5.4 g/dL). The median follow-up time was 22 months (1–91 months). The causes of PRCA were as follows: primary (52 cases, 65.8%), thymoma-associated (10 cases, 12.7%), and large granular lymphocyte leukaemia (LGL)-associated (11 cases, 13.9%), parvovirus B19 infection (2 cases, 2.5%), major ABO-mismatched allogeneic haematopoietic stem cell transplantation (2 cases, 2.5%), connective tissue disease (1 case, 1.3%), and anti-erythropoietin antibody-mediated (1 case, 1.3%).

3.2. Treatment

We administered immunosuppressive treatment consisting of CsA and/or CS initially. The minimum period required for an evaluation of the response of an agent was defined as 4 weeks (range, 1–6 months). The initial response rate and CR rate were not significantly different between CsA group and CS group (76.2% vs 47.6%, $P = .057$; 42.9% vs 19.0%, $P = .095$); CsA combined with CS group had higher CR rate than did CS group (61.3% vs 19.0%, $P = .003$), although response rate was not significantly different between 2 groups (71.0% vs 47.6%, $P = .089$) (Table 1).

More patients in CsA combined with CS group achieved CR than did the patients in group of CS at 3, 6, and 12 months (54.8% vs 21.1%, $P = .019$; 63.3% vs 21.1%, $P = .004$; 62.1% vs 16.7%, $P = .002$) (Table 2).

Besides, the median time of CsA combined with CS group, CS group, and CsA group were 1 month (range, 1–6 months), 2 months (range, 1–3 months), 3 months (range, 1–3months), respectively. By Kaplan–Meier method, patients achieved CR faster in CsA combined with CS group than those in CS group or CsA group ($P = .010$) (Fig. 1).

Table 1

Influence factors of efficacy in Pure Red Cell Aplasia patients.

Category and variable	Efficacy		*P* value
	CR+PR	NR	
Age, y			.605
>60	20	12	
<60	28	13	
Gender			.310
Male	19	13	
Female	29	12	
Primary vs secondary			.280
Primary	33	14	
Secondary	15	11	
Initial induction therapy	CR+PR	NR	
CsA	16	5	.057
CS	10	11	
Initial induction therapy	CR	PR+NR	
CsA	9	12	.095
CS	4	17	
Initial induction therapy	CR+PR	NR	
CsA+CS	22	9	.089
CS	10	11	
Initial induction therapy	CR	PR+NR	
CsA+CS	19	12	.003
CS	4	17	

CR = complete remission, CS = corticosteroids, CsA = cyclosporine A, NR = no response, PR = partial remission.

Table 2

Clinical efficacy of different initial therapies.

	CS (n=21)		CsA (n=21)		CS+CsA (n=31)	
	CR/PR	NR	CR/PR	NR	CR/PR	NR
Time						
1 mo	2/8	11	2/11	8	10/9	12
3 mo	4/4	11	8/7	5	17/5	9
6 mo	4/4	11	7/7	5	19/2	9
12 mo	3/4	11	5/7	5	18/2	9
etiology						
Primary (n=47)	3/5	7	6/3	3	14/2	4
Secondary (n=26)	1/1	4	3/4	2	5/1	5

CR = complete remission, CS = corticosteroids, CsA = cyclosporine A, NR = no response, PR = partial remission.

3.3. Primary and secondary PRCA

The initial response of primary and secondary PRCA is shown in Table 2.

In primary PRCA, CR and PR were achieved in 23 patients (48.9%) and 10 patients (21.3%) respectively crossing the different treatment regimens. Including relapsed and refractory patients, there were 9 deaths (19.1%) in total. The response rates and CR rates of CS and CsA group were similar (53.3% vs 75.0%, $P=.424$; 20.0% vs 50.0%, $P=.127$). The CR rate was higher in CsA combined with CS group than in CS group (70.0% vs 20.0%, $P=.006$).

In secondary PRCA, 9 of 26 patients achieved CR (34.6%, 3 LGL and 6 thymoma), and 6 patients achieved PR (23.1%, 2 LGL, 2 thymoma, and 2 others) crossing the different treatment regimens. In general, 8 patients were still transfusion-dependent and 6 patients were dead (23.1%, 4 thymoma, 1 LGL, and 1 other). No significant differences were found in response rate and CR rate between CS group and CsA group (33.3% vs 77.8%, $P=.136$; 16.7% vs 33.3%, $P=.604$). Though CsA combined with CS tended to produce higher CR rate than CS in secondary PRCA, it did not reach statistical difference (45.5% vs 16.7%, $P=.333$).

Regardless of the treatment regimens, we did not find significant differences in initial response rates and CR rates between primary and secondary PRCA (70.2% vs 57.7%, $P=.280$; 48.9% vs 34.6%, $P=.473$).

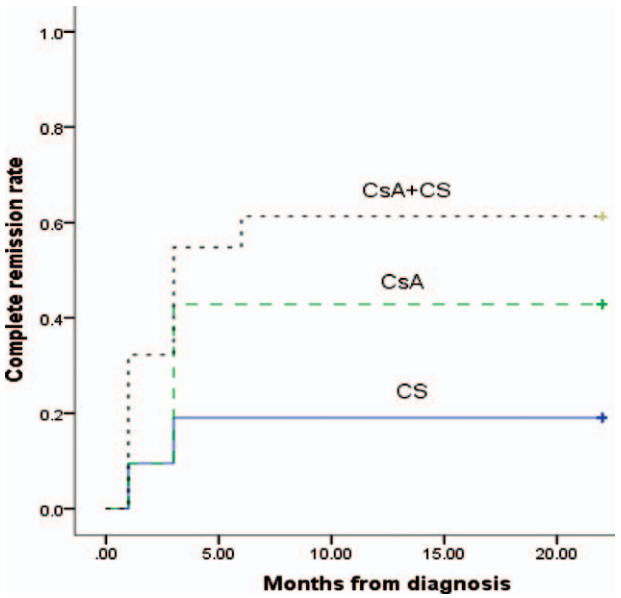

Figure 1. Complete remission rates of different initial therapies. CR rates for patients treated with CsA+CS, CsA, or CS were calculated by method of Kaplan–Meyer. CsA combined with CS achieved CR faster than CS group or CsA group (median time, 1 vs 2 vs 3 mo, $P=.010$). CS = corticosteroids, CsA = cyclosporine A, CR = complete remission.

3.4. Relapsed and refractory PRCA

Among the 25 patients who failed to respond to initial remission induction therapy, 5 patients achieved CR/PR by changing regimens. Including patients who had crossed over from other treatment groups, the cumulative response rate of all evaluable patients was 72.6% (53/73). In 48 patients who responded to the initial therapy, 26 patients relapsed because of discontinuation or tapering therapy. In these 26 relapsed patients, 19 patients regained response by increasing the dose of original regimens or changing to other immunosuppressive therapy, while the other 7 patients did not respond to reinduction therapy and 4 of them died eventually. In 5 patients who responded to the salvage therapy, 1 relapsed during the tapering period, and failed to respond to other immunosuppressive agents, was still in need of transfusion. The response rate of initial induction, reinduction therapy for relapsed PRCA were similar (65.8% vs 70.4%, $P=.663$).

The median time from therapy to relapse was 16 months (range, 3–69 months). Fourteen patients relapsed by reduction of CS or CsA, and 13 patients relapsed due to discontinuation of therapy. The estimated median relapse-free survival was 18 months (range, 9–69 months), 16 months (range, 3–33 months), 12 months (range, 10–36 months) in CsA group (n=6), CsA combined with CS group (n=17), and CS group (n=4). The duration of initial remission was not different among CsA, CsA combined with CS, and CS groups ($P=.265$).

In 20 refractory patients who failed 2 regimens including initial induction and salvage therapy, 10 patients were still transfusion-dependent, and 10 patients were dead.

3.5. Factors impacting the clinical efficacy

We analyzed the factors that impact the clinical efficacy, and found that therapeutic efficacy was not significantly different in the groups divided by age ($P=.605$), sex ($P=.310$), etiology ($P=.280$), or regimens of CsA+CS versus CS ($P=.089$) (Table 1). By univariate analysis, CR rate was affected by age ($P=.049$), sex ($P=.030$), and regimen (CsA+CS vs CS) ($P=.005$). By multivariate analysis, CsA combined with CS regimen ($P=.009$) and primary PRCA ($P=.019$) were the factors affecting CR rate compared with CS regimen and secondary PRCA, respectively (Table 3).

3.6. Adverse effects and overall survival

The adverse effects during immunosuppressive treatments were recurrent infection (23/73, 31.5%), and impaired liver and renal function. Pulmonary infection was the most frequent type of infection (18/73, 24.7%). Fifteen patients died during follow-up. The causes of death were infection, heart failure, respiratory

Table 3

Influencing factors of initial complete remission for Pure Red Cell Aplasia patients.

Category and variable	*P* value	
	Univariate	Multivariate
Age, y (>60 vs ≦60)	0.049	.097
Gender (male vs female)	0.030	.110
etiology (primary vs secondary)	0.561	.019
Therapy (CsA+CS vs CS)	0.005	.009

CS = corticosteroids, CsA = cyclosporine A.

failure, and unknown reasons. No significant differences in the rate of infection were noted among the groups of CS, CsA, and CsA combined with CS (33.3% vs 38.1% vs 25.8%, $P = .631$). Survival time was not significantly different between the primary and secondary forms of PRCA ($P = .925$) (Fig. 2).

We analyzed potential risk factors for death. Age, gender, and the complete response to induction therapy were identified as risk factors for death in PRCA ($P = .010$, $P = .046$, $P = .001$). Relapse of anemia was not a risk factor for death ($P = .453$) (Table 4).

Complete remission to induction therapy ($P = .035$) other than age ($P = .115$), sex ($P = .147$), or etiology ($P = .500$) was identified to affect survival by multivariate analysis (Cox regression analysis) (Table 5). Cumulative survival by Kaplan–Meier also suggested that complete remission to induction therapy impacted the death ($P = .004$) (Fig. 3).

4. Discussion

We report the detailed clinical characteristics and treatment outcomes for adult patients with PRCA. PRCA has been proposed to be mediated by $CD8^+$T cells, γδT cells, large granular lymphocytes, antierythropoietin antibodies, and anti-erythropoietin receptor antibodies.[11–16] Immunosuppressive therapy has been used as the initial treatment for acquired PRCA. CS and CsA were the leading drugs for treatment of PRCA.

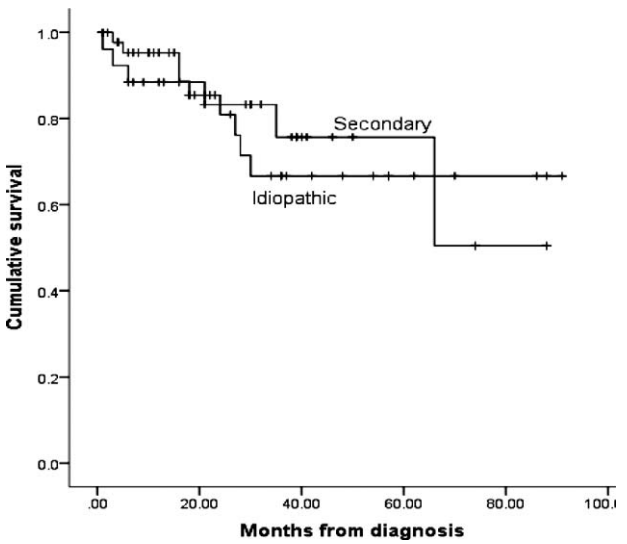

Figure 2. Cumulative survival of PRCA patients. There was no significant difference in survival time between the primary (n = 47) and secondary (n = 26) forms of PRCA ($P = .925$) by Kaplan–Meier method. PRCA = pure red cell aplasia.

Table 4

Factors related to survival.

Category and variable	Alive (n = 58)	Death (n = 15)	*P* value
Age, y			.010
>60	21	11	
<60	37	4	
Gender			.046
Male	22	10	
Female	36	5	
Primary vs secondary			.691
Primary	38	9	
Secondary	20	6	
Complete remission to induction therapy			
CR	31	1	.001
PR/NR	27	14	
Relapse*	Alive (n = 43)	Death (n = 5)	
Yes	22	4	.453
No	21	1	

CR = complete remission, NR = no response, PR = partial remission.
* Survival of relapsed patients who responded to induction therapy.

Mamiya et al[5] reviewed the clinical features of 150 patients with acquired PRCA in Japan. The response rate to CsA was 87% in the patients with primary PRCA and 73% in secondary PRCA, respectively. They recommend CsA as first-line therapy for the disease. It is controversial whether CsA has better efficacy than CS in treatment of PRCA.[9,10] Our single-center experience showed that the patients treated with CsA tended to have a better response than those treated with CS (response rate 70.0% vs 50.0%, $P = .313$; CR rate 33.3% vs 28.6%, $P = 1.000$), yet it did not reach statistical difference.[17] We expanded the sample size of cases and prolonged the observation time in the current study, still no differences were found in response rate and CR rate between CS and CsA ($P = .057$; $P = .095$), further confirming the Japanese group's results.[10] However, higher CR rate was achieved in the group of CsA combined with CS than CS alone ($P = .003$). Besides, the patients achieved CR faster in CsA combined with CS group than in CS group or CsA group (median time, 1 vs 2 vs 3 months, $P = .010$).

The CR rate of CsA combined with CS was higher than CS group ($P = .006$) in primary PRCA, but it was not the case in secondary PRCA (45.5% vs 16.7%, $P = .333$). Etiology of secondary PRCA includes a humoral factor (e.g., IgG antibody) suppressing the erythroid lineage, antibodies against erythropoietin, and cell-mediated suppression (including T-cells, large granular lymphocytes, and natural killer cells).[4,18] Considering the different causes, increasing evaluable patient cases and long-term follow-up are needed to explore more specific regimens for different types of secondary PRCA. We suggest choosing CsA

Table 5

Multivariate analysis: factors related to survival.

Category and variable	*P* value
Age, y (>60 vs ≦60)	.115
Gender (male vs female)	.147
etiology (primary vs secondary)	.500
Complete remission to induction therapy (CR vs PR+NR)	.035

CR = complete remission, NR = no response, PR = partial remission.

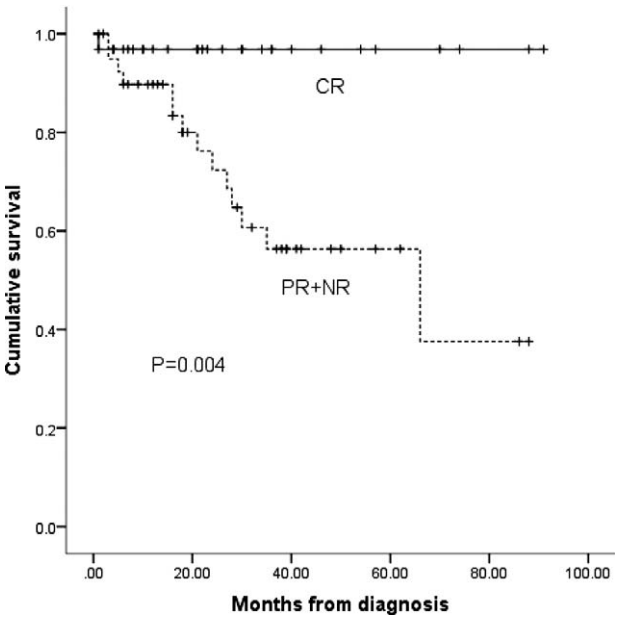

Figure 3. Cumulative survival of PRCA patients. Overall survival of the patients achieved complete remission by induction therapy (n = 32) was higher than patients who gained partial remission and failed to initial induction therapy (n = 41) ($P = .004$) by Kaplan–Meier method. PRCA = pure red cell aplasia.

combined with CS as initial induction therapy, especially in primary PRCA.

The main reason of relapse was discontinuation or tapering therapy. Sawada et al[10] reported that discontinuation of maintenance CsA therapy was strongly correlated with relapse in patients with primary PRCA. A total of 27 patients relapsed because of discontinuation or tapering therapy in our study. Nineteen patients regained response by increasing the dose of original regimens or changing to other immunosuppressive therapy. Guidelines for the diagnosis and management of adult aplastic anemia published in 2016 recommend that a slow tapering of the drug (25 mg every 2–3 months) can be started after at least a further 12 months of therapy, to reduce the risk of later relapse.[19] Maintenance CsA-containing regimens seem to be important to prevent relapse, continuous and careful follow-up is required for patients receiving long-term CsA therapy. Hirokawa et al[20] demonstrate that response of relapsed PRCA to immunosuppressive therapy was inferior to those of previously untreated patients, except for those with LGL-associated PRCA ($P = .679$). However, response rates of initial induction, reinduction therapy for relapsed PRCA were similar in our report (65.8% vs 70.4%, $P = .663$), which was not consistent with the observation of the Japanese nationwide cohort study. Patients in our study received systemic therapy and follow-up in 2 centers, while Japanese nationwide surveys from 185 patients with chronic PRCA were collected from 45 institutions, this might be the reason of the difference of responses to reinduction therapy for relapsed PRCA between Japanese and our study.

A latest report of long-term outcome of patients with acquired chronic PRCA following immunosuppressive therapy in Japan analyzed potential risk factors for death, including age, gender, etiology, response to induction therapy, and relapse of anemia. Refractoriness to induction immunosuppressive therapy and relapse of anemia were found to be associated with death ($P = .002$, $P < .001$).[20] We also found that complete remission to induction therapy was associated with survival ($P = .035$). But our study did not observe a significant contribution of relapse of anemia to the risk of death. The difference in responses to reinduction therapy for relapsed PRCA between Japanese survey and our study might lead to different results of potential risk factors for death. Increasing evaluable cases and long-term follow-up would be required to determine the correlation.

5. Conclusion

In conclusion, adult patients with acquired pure red cell aplasia showed a good response to either corticosteroids or cyclosporine A. Our study suggests that CsA combined with CS produced faster and higher CR rate in adult patients with PRCA, and might serve as the initial induction therapy for these patients.

Author contributions

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