

Original Article

Cyclosporine, prednisone, and high-dose immunoglobulin treatment of angioimmunoblastic T-cell lymphoma refractory to prior CHOP or CHOP-like regimen

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Abstract

Angioimmunoblastic T-cell lymphoma (AITL) is a rare, distinct subtype of peripheral T-cell lymphoma, possessing an aggressive course and poor prognosis with no standard therapy. Twelve patients who have failed at least two initial CHOP or CHOP-like regimens were enrolled in this study and treated with individualized cyclosporine (CsA), prednisone (PDN), and monthly, high-dose intravenous immunoglobulin (HDIVIG). The dose of CsA was adjusted individually based on the blood trough concentration of CsA and renal function. All patients were examined for response, toxicity and survival. The most significant toxicities (\geq grade 2) were infection (16.7%), renal insufficiency (8.3%), hypertension (8.3%), diabetes (8.3%) and insomnia (16.7%). Discontinuation of treatment occurred in one patient (8.3%) due to grade 3 renal toxicity and subsequent grade 4 pulmonary infection. Treatment-related death was not observed. The overall response rate was 75.0% (complete response, 33.3%; partial response, 41.7%). With a median follow-up of 25.5 months, the median duration of response was 20 months (range, 12 to 49 months) and the median progression-free survival (PFS) was 25.5 months (range, 10 to 56 months). The 2-year PFS rate was 81.5%. Our findings indicate the combination of CsA, PDN and HDIVIG is an effective salvage regimen for refractory or relapsed AITL with predictable and manageable toxicity.

Key words Cyclosporine, immunoblastic lymphadenopathy, intravenous immunoglobulin, prednisone, therapeutics.

Angioimmunoblastic T-cell lymphoma (AITL) is a rare distinct subtype of peripheral T-cell lymphoma, accounting for approximately 4.0% of T-cell non-Hodgkin's lymphomas (NHL) in South China. With an aggressive course and poor prognosis, most patients

present with advanced-stage disease at diagnosis.

There is no standard therapy for AITL, especially for refractory or relapsed cases. Patients do not respond well to conventional chemotherapy with a median survival of less than 36 months and a 5-year survival rate of 30.0% to 35.0%^[1,2]. In addition, the majority of patients who have failed initial conventional chemotherapy usually respond poorly to salvage chemotherapy and cannot tolerate more intensive chemotherapy which may increase the risk of infectious morbidity in an immune-compromised population^[3,4].

AITL patients were responsive to immunosuppressive agents such as prednisone (PDN) and cyclosporine (CsA)^[5]. However, progressive or relapsed disease frequently occurred in a short-term remission after dose reduction or discontinuation of PDN or CsA^[6,7]

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and CsA was prematurely discontinued in some cases due to treatment-related renal or infectious complications^[8]. Considering the successful combined modality of immunosuppressive therapy with CsA and PDN-based regimens in preventing acute rejection in organ transplantation and the effect of intravenous immunoglobulin on preventing infections in patients with chronic lymphocytic leukemia, we postulated that patients who have failed first-line CHOP (cyclophosphamide, doxorubicin, vincristine, and PDN) or CHOP-like regimens might benefit from long-term treatment with a combination of CsA, PDN, and a monthly high-dose intravenous immunoglobulin (HDIVIG), which may help reduce the risk of infection during therapy.

Patients and Methods

Study design and objectives

In AITL patients who have failed initial CHOP or CHOP-like treatment regimens including CEOP (cyclophosphamide, vincristine, epirubicin, and PDN) and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), we conducted this trial to determine the overall response rate (ORR) with a combined regimen of CsA, PDN, and monthly HDIVIG. ORR was defined as a complete response (CR), an unconfirmed complete response (CRu), or a partial response (PR). Secondary objectives included safety, progression-free survival (PFS), and duration of response (DR). Informed consent has been obtained from each subject and/or guardians before study.

Patient selection

Patients who aged at least 18 years and have failed two or more cycles of initial CHOP or CHOP-like regimens were enrolled at the Sun Yat-sen University Cancer Center between January 2006 and December 2010. Cases of AITL were hematopathologically confirmed in accordance with the WHO classification^[9] at diagnosis and relapse. The inclusive criteria included measurable disease with a lymph node or tumor mass ≥ 2 cm in diameter, a life expectancy of ≥ 3 months, an Eastern Cooperative Oncology Group performance status of 0 to 2, an absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$, a platelet count $\geq 50\,000/\mu\text{L}$, a hemoglobin count ≥ 8 g/dL, a serum creatinine concentration < 150 $\mu\text{mol/L}$, a creatinine clearance > 80 mL/min, a serum bilirubin concentration ≤ 1.5 ULN, a serum cholesterol concentration ≤ 3.5 g/L, a triglyceride level ≤ 400 mg/dL, and no human immunodeficiency virus (HIV) infection or active central nervous system lymphoma.

Evaluation and treatments

Baseline evaluation included medical history, physical examination, complete blood count, serum lactate dehydrogenase (LDH), serum electrolytes and clinical chemistry, bone marrow aspiration/biopsy, and disease staging using contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET/CT). Patients were classified according to the Ann Arbor staging system^[10]. Blood trough concentrations of CsA (FPIA assays) and plasma Epstein-Barr virus (EBV) DNA levels were also monitored. Patients were treated with a combination of CsA, PDN, and monthly HDIVIG for 5 years, or until disease progression or unacceptable toxicity. CsA was initially given at an oral dose of 3 mg/kg per day, twice daily; PDN was given at an oral dose of 60 mg/m² per day from day 1 to day 5, repeated every month; and 15.0 g of IVIG was administered as an intravenous infusion over 60 min, repeated monthly. Given that renal toxicity is the main cause of discontinuation of CsA treatment^[8], if patients developed elevated serum creatinine concentration before treatment, the dose of CsA was adjusted to 2.5 mg/kg per day for initial treatment. Dose adjustment of CsA was implemented to achieve blood trough levels of CsA between 75 ng/mL and 150 ng/mL, and normal serum creatinine during treatment. If patients developed a grade 2 non-renal toxicity, treatment continued without dose adjustment and some agents should be used to control corresponding toxicities. If toxicity is persistent after treatment, dose reduction by 25% should be considered. Treatment was withheld if serum creatinine concentration was > 178 $\mu\text{mol/L}$, neutrophil count was $< 1000/\mu\text{L}$, platelet count was $< 50\,000/\mu\text{L}$, or grade 3 or 4 nonhematologic toxicities were observed, and reinitiated at a reduced dose by 25% if patients recovered serum creatinine concentration to ≤ 130 $\mu\text{mol/L}$, ANC to $\geq 1000/\mu\text{L}$, a platelet count $\geq 50\,000/\mu\text{L}$, or a grade 0 to 1 nonhematologic toxicity was observed within 3 weeks. If a similar severity of toxicity occurred at the reduced dose, the study treatment was terminated.

Response criteria

Responses and toxicities were assessed after one month, and thereafter every two months for the first year, every three months for the next two years and every six months for the last two years, or until death, disease progression or change of treatment. Response and progression were assessed based on the International Working Group Response Criteria for NHL^[10], using the same imaging method (CT, MRI, or PET/CT scan) to establish baseline tumor measurements. The severity of adverse events was determined using the National

Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0.

Statistical analyses

The primary end point of the study was ORR, and the secondary end points were safety, PFS, and DR. Patients were classified with CR, CRu, PR, stable disease (SD), or progressive disease (PD). ORR was calculated as the number of patients achieving CR, CRu, or PR. PFS was defined as the time from first dose of study drug to first documentation of disease progression or death. DR was calculated as the time from first documentation of best response (CR, CRu, or PR) to first documentation of disease progression or death. Statistical analyses for patients' characteristics, response rates, DR and adverse events were descriptive. The PFS was estimated using the Kaplan-Meier method, and two-sided 95% confidence intervals (CIs) were calculated using the Brookmeyer-Crowley nonparametric method^[11]. All statistical analyses were performed using SPSS16.0 software.

Results

Patient characteristics and disposition

Twelve consecutive patients were registered in this study between January 2006 and December 2010. Baseline characteristics of the subjects are listed in Table 1. Median age was 64 years (range, 52 to 76 years). Eight (66.7%) were men and 4 (33.3%) were women. All patients developed generalized lymphadenopathy and elevated LDH. Most patients had an advanced disease (IPI ≥ 3 , 75.0%; stage IV, 75.0%; bone marrow infiltration, 25.0%; and B symptoms, 66.7%). Eight (66.7%) of 12 patients experienced anemia and an enlarged liver and/or spleen, respectively. Three (25.0%) experienced hypoproteinemia (serum albumin level < 35 g/L). Nine (75.0%) were refractory to initial chemotherapies and 3 (25.0%) had disease relapse. Eight (66.7%) were treated with CHOP regimens and 4 (33.3%) with CHOP-like regimens. Infection was observed in 10 (83.3%) patients.

Table 1. Baseline characteristics of 12 AITL patients who have failed CHOP or CHOP-like regimens

Characteristic	Patient number
Sex	
men	8
women	4
Serum LDH level >ULN	12
Stage	
III	3
IV	9
Serum beta-2 microglobulin level	12
IPI ≥ 3	9
Extranodal involvement >1	6
Lymphadenopathy	12
Presence of B symptoms	8
Hepatomegaly	3
Splenomegaly	5
Bone marrow involvement	3
Anemia	8
Serum albumin level < 35 g/L	3
Prior treatment	
CHOP regimens	8
CHOP-like regimens	4
Relapsed disease	3
Refractory to initial treatment	9
Infection during chemotherapy	10

AITL, angioimmunoblastic T-cell lymphoma; PS, performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal; IPI, international prognostic index; CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisone.

Responses

The outcomes of treatment in 12 patients are shown in Table 2. The treatment was still ongoing in 8 patients in December 2010. One patient with CR was lost to follow-up after an 18-month treatment, 1 with coronary heart disease before treatment died of a heart attack after a 20-month treatment, and treatment was discontinued in 2 patients (one with PD, the other with grade 3 renal dysfunction and subsequent grade 4 pulmonary infection). The ORR was 75.0%, including 4 (33.3%) patients who had CR and 5 (41.7%) who had PR. In the refractory subgroup, patients had an ORR of 66.7% (6 of 9 patients), a CR rate of 22.2% (2 of 9 patients), and a PR rate of 44.0% (4 of 9 patients); whereas in the relapsed subgroup, patients had an ORR of 100.0%, a CR rate of 66.7% (2 of 3 patients), and a PR rate of 33.3% (1 of 3 patients). This regimen appeared more effective in a relapse setting than in refractory disease. Two of 12 (16.7%) patients experienced an SD, 1 (8.3%) had a PD after 10-month

treatment. With a median follow-up of 25.5 months, the median DR was 20 months (range, 12 to 49 months) and the median PFS was 25.5 months (range, 10 to 56 months). The 2-year PFS rate was 81.5%. Figure 1 shows the curve of PFS by the Kaplan-Meier analysis.

Of the 4 patients who obtained CR, 3 were still in remission after a 56-, 46-, and 30-month treatment, respectively, whereas the remaining 1 patient with CR was lost to follow-up after 18 months. Three of the 5 patients with PR remained PR after 32-, 26-, and 24-month treatments, respectively; 1 died of a heart attack 20 months after treatment; and the remaining 1 did not continue the treatment due to grade 3 renal toxicity and subsequent grade 4 pulmonary infection.

Toxicity

This regimen was generally well tolerated and all patients completed more than 10 months (range, 10 to 56 months; median, 25.5 months) of treatment. Treatment-related toxicities are listed in Table 3. No NCI

Table 2. Outcomes of 12 patients with refractory or relapsed AITL treated with a combination of CsA and PDN

Group	ORR	CR	PR
All patients (<i>n</i> = 12)	9 (75.0)	4 (33.3)	5 (41.7)
Refractory disease (<i>n</i> = 9)	6 (66.7)	2 (22.3)	4 (44.4)
Relapsed disease (<i>n</i> = 3)	3 (100.0)	2 (66.7)	1 (33.3)

The values are presented as numbers of patients, with percentages in parentheses. PDN, prednisone; CsA, cyclosporine. Other abbreviations as in Table 1.

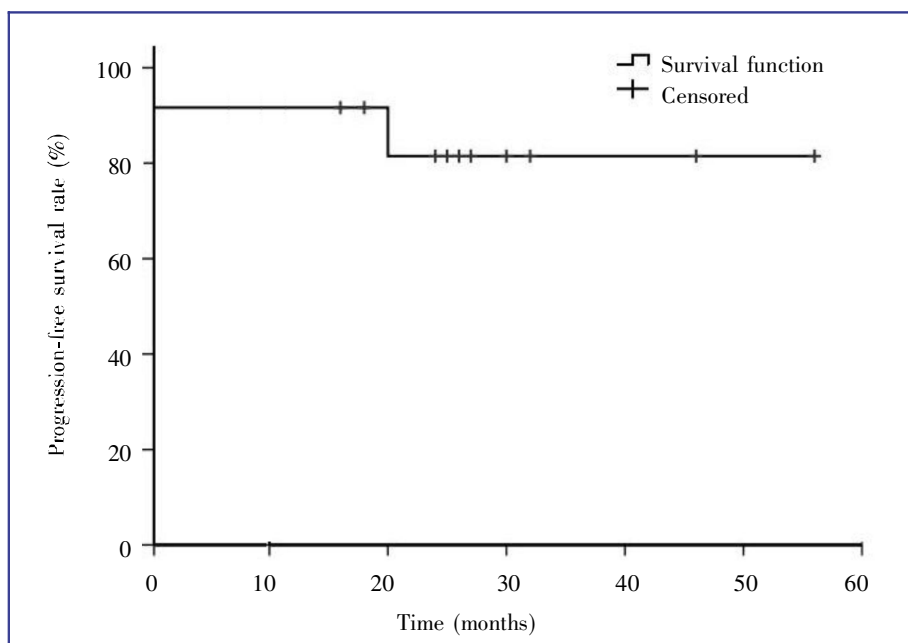


Figure 1. Kaplan-Meier curve of progression-free survival (PFS) for 12 patients treated with cyclosporine (CsA), prednisone (PDN), and intravenous immunoglobulin (IVIg). Patients without disease progression or lost to follow-up were censored at the last assessment for tumor response. The 2-year PFS rate was 81.5%.

grades 2 to 4 hematologic toxicity was observed. The median blood trough concentration of CsA was 108 ng/mL (range, 68 to 365 ng/mL), which is showed in Figure 2.

In all patients, termination of treatment occurred in 1 patient due to grade 3 renal dysfunction and subsequent grade 4 pulmonary infection. Dose reduction was required in 4 patients due to a blood trough level of CsA >150 ng/mL (2 of 4 patients with temporary grade 1 elevation of serum creatinine). No treatment-related death was recorded.

One patient with a grade 2 gastrointestinal infection

discontinued chemotherapy and were treated with antibiotics and anti-diarrheal agents were employed. This patient recovered and continued chemotherapy one week later. One patient with grade 2 hypertension received antihypertensives without a dose reduction of CsA and PDN. Thus, this patient achieved a CR for 25 months with hypertension under control. One patient with grade 2 diabetes was treated with a reduction of PDN by 25.0%, acarbose, and a diabetic diet and achieved a CR for 14 months. One elderly patient with 50-year asthma and 5-year coronary heart disease discontinued the investigative regimen due to a grade 3 renal toxicity

Table 3. Toxicities of treatment with CsA, PDN, and IVIG in 12 patients with refractory/relapsed AITL

Adverse event	Number of patients (%)
Infection	2 (17)
Grade 2 (GI tract)	1 (8)
Grade 4 (Pulmonary)	1 (8)
Hypertension	1 (8)
Grade 2	1 (8)
Renal insufficiency	3 (25)
Grade 1 (elevated creatinine)	2 (17)
Grade 3 (elevated creatinine)	1 (8)
Diabetes (Grade 2)	1 (8)
Insomnia (Grade 2)	2 (17)
Gum hyperplasia (Grade 1)	2 (17)
Diarrhea (Grade 1)	2 (17)
Influenza-like symptoms	6 (50)

GI, gastrointestinal. Other abbreviations as in Tables 1 and 2.

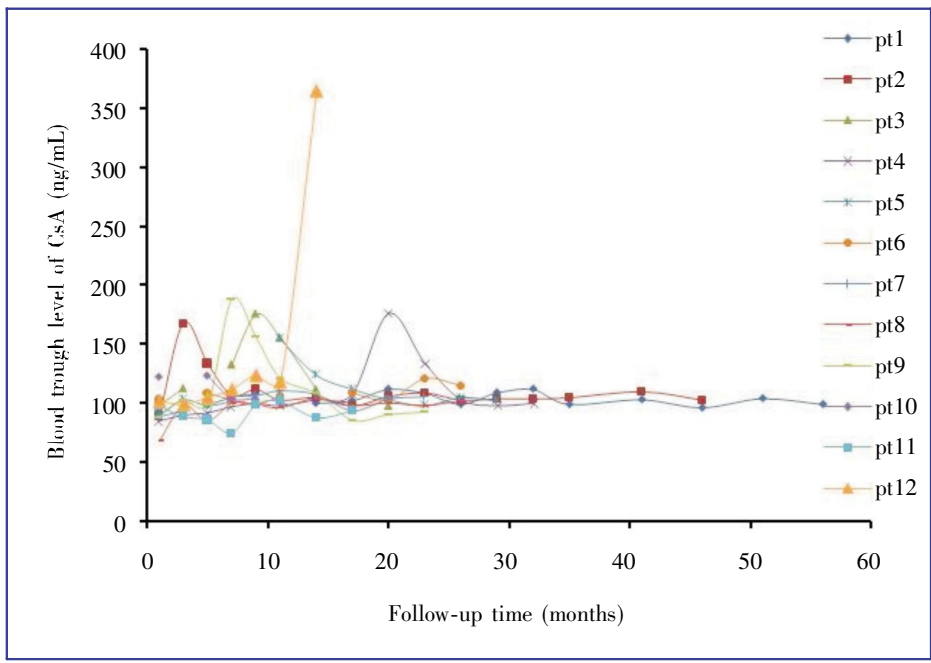


Figure 2. Curves of blood trough levels of CsA in 12 patients with refractory/relapsed angioimmunoblastic T-cell lymphoma (AITL) treated with CsA, PDN, and IVIG. The trough levels of blood CsA were tested by FPIA assays and the dose of CsA was titrated based on blood trough concentration of CsA >150 ng/mL or <75 ng/mL, renal dysfunction, and other severe complications.

(serum creatinine of 354 $\mu\text{mol/L}$ and blood trough concentration of CsA of 365 ng/mL) and a subsequent grade 4 pulmonary infection, and were treated with antibiotics, HDIVIG, and mechanical ventilation. All patients suffering these adverse events had a complete recovery after treatment within three weeks.

The plasma levels of EBV-DNA in all patients were frequently monitored. Plasma EBV-DNA levels in 4 (33.3%) of 12 patients were detectable (1 CR, 2 PR, 1 PD). One PR patient developed a significant increase of plasma EBV-DNA level (before therapy, 3.56×10^3 copies/mL; 16 months after therapy, 16.8×10^3 copies/mL) during treatment, but no evidence of disease progression was found.

Discussion

Chemotherapeutic regimens have been investigated for the treatment of primary or relapsed AITL, but no standard chemotherapeutic regimen has been established. Combined chemotherapy has failed to increase the response and survival rate to more than 30.0%^[12]. These regimens include VAP (vincristine, doxorubicin, and prednisolone)^[13], CHOP^[14], CHOP-like regimens^[15], and COPBLAM/IMVP-16 (cyclophosphamide, vincristine, PDN, bleomycin, doxorubicin, procarbazine, ifosfamide, methotrexate, and etoposide)^[1]. The poor outcomes of patients treated with conventional chemotherapy necessitate the investigation into some other agents and novel approaches, including low-dose methotrexate (combined with corticosteroids), fludarabine, cladribine, interferon-alpha, thalidomide, lenalidomide, alemtuzumab, rituximab (combined with CHOP), and bevacizumab^[12,16]. Unfortunately, there is no evidence that any of these agents improves outcome compared with conventional anthracycline-based chemotherapy. Although most of these agents are successful in achieving a CR or PR in many AITL patients, the responses were not typically sustained and the disease relapsed in majority of patients after a short-term remission. Thus, it remains an important goal to develop new agents and novel regimens for patients with AITL.

AITL is heterogeneous and can, at times, be treated solely with corticosteroids or other immunosuppressive agents. PDN alone or combined with other chemotherapeutic agents is effective for this disease under first- or second-line settings^[1,17,18], but relapse generally follows in a short-term remission^[6]. CsA, an immunosuppressive agent which can inhibit T-cell activation by binding cyclophilin in T cells, thus preventing the nuclear translocation of the nuclear factor of activated T cells (NF-AT), has also been effective in patients with relapsed AITL following treatment with

steroid or multi-agent chemotherapy^[8]. However, progression or relapse of AITL after dose reduction or discontinuation of CsA was also observed in case report studies and some patients with AITL could not tolerate the CsA-related renal toxicities and infection^[7,19,20]. Therefore, long-term immunosuppressive therapy may be a better modality of treatment for refractory or relapsed AITL, and the avoidance or reduction of CsA-related renal toxicity and serious infection may be critical in warranting long-term immunosuppression.

In a retrospective study of 12 AITL patients treated with single-agent CsA^[8], the initial dose of CsA was 6 to 10 mg/kg per day; the blood concentration of CsA was not monitored. Two of 12 (16.7%) patients developed acute infections and 1 died shortly after active treatment, 3 (25.0%) developed CsA-related renal insufficiency during therapy and 3 (25.0%) discontinued treatment with CsA due to CsA-related renal toxicity. The toxicity findings of the present study suggest that a carefully preventive management of CsA-related infection and renal toxicity may be critical to improve the clinical outcome of AITL patients treated with CsA. Previous studies have shown that IVIG prophylaxis could significantly reduce the occurrence of major infection and clinically documented infection in chronic lymphocytic leukemia and multiple myeloma^[21-23]. Based on prominent immune dysfunction associated with AITL, potential persistent immunosuppression of long-term treatment with CsA and PDN, all patients were initially given monthly HDIVIG to help reduce the potential risk of severe systemic infection. Considering frequent discontinuation of CsA due to CsA-related renal insufficiency^[8] and the use of CsA in transplantation patients for controlling organ rejection^[24], we prematurely adjusted the dose of CsA, predicated on the blood trough concentration of CsA and elevated serum creatinine before and during treatment. As could be expected, toxicity of the combination treatment with CsA, PDN, and HDIVIG were predictable and manageable with no treatment-related death. The most significant toxicities were infections, renal dysfunction, hypertension, diabetes, and insomnia. The results of our study have shown the addition of PDN to CsA combined with monthly HDIVIG did not significantly increase the risk of infection, with an incidence of 16.7% as compared to 16.7% reported by Advani *et al.*^[8]. Interestingly, the incidence of grades 2 to 4 renal insufficiency (grade 3 in 1 patient, 8.3%) was significantly lower as compared to 25.0% reported by Advani *et al.*^[8], possibly achieved by individualized dose adjustment of CsA based on the blood CsA concentration and renal dysfunction. The addition of PDN may help reduce the dose of CsA. Furthermore, our findings demonstrated a good response in refractory or relapsed AITL patients treated with combination of CsA, PDN, and HDIVIG, with an ORR of 75.0%. Of our

12 patients, 4 (33.3%) achieved a CR and 5 (41.7%) achieved a PR. With a median follow-up of 25.5 months, the median DR was 20 months (range, 12 to 49 months) and the median PFS was 25.5 months (range, 10 to 56 months). The 2-year PFS rate was 81.5%. The results of our study demonstrate that the combination of CsA, PDN, and monthly HDIVIG was effective in treating patients with refractory or relapsed AITL, with predictable and manageable toxicities. Notably, an individualized dose schedule of CsA based on the blood concentration of CsA and renal insufficiency was important for patients with renal dysfunction.

A concern of long-term immunosuppressive treatment with CsA and PDN is the potential activation of EBV. EBV has been found in the cellular infiltration in most AITL cases as compared to normal lymph nodes or unspecified peripheral T cell lymphoma^[25,26]. If EBV is responsible for the genesis and progression of AITL, long-term immunosuppressive treatment with CsA and PDN can potentially exacerbate disease progression. However, the results reported by Lee *et al.*^[27] indicate that EBV-positivity has no correlation with clinical outcome. In our study, plasma EBV-DNA levels in 4 of 12 (33.3%) patients were detectable. One PR patient developed a significant increase of plasma EBV-DNA after treatment, but no evidence of disease progression was found. Further investigation in a large population is

required to elucidate this concern.

Conclusions

This is the first study to investigate the efficacy and safety of combinatorial CsA, PDN and monthly HDIVIG therapy in patients with refractory or relapsed AITL. Our data suggest that this regimen is an effective salvage treatment, with predictable and manageable toxicities. Individualized dose adjustment of CsA, based on the blood concentration of CsA and renal function, plays an important role in the reduction of CsA-related renal dysfunction. Treatment with monthly HDIVIG can significantly reduce the risk of severe infection during therapy, helping patients tolerate long-term immunosuppressive treatment. Further studies are needed to determine the optimal duration of this combined regimen.

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