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Original Article

Outcomes of 48 patients with primary angioimmunoblastic T-cell lymphoma in real-world clinical practice: a single-center experience

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Abstract: Angioimmunoblastic T-cell lymphoma (AITL) is a rare cancer of the lymphatic system. There is no effective chemotherapy regimen for long-term survival. The traditional chemotherapy regimen consists of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP). This study evaluated the outcomes of a cyclophosphamide, doxorubicin, vincristine, prednisolone, and thalidomide (CHOP-T) regimen for patients with primary AITL. Clinical data of 48 primary AITL patients treated with CHOP-T or CHOP regimens were retrospectively analyzed. The 2-year overall survival (OS) and progression-free survival (PFS) rates of all patients were 52.8% and 36.6%, respectively. The 2-year OS rates of the CHOP-T group were better than that of the CHOP group (70.6% vs. 44.6%, P=0.045). However, this did not translate into significantly better PFS (P=0.122) or complete remission (CR) rates (P=0.068). Multiple-factor analysis showed that positive Coombs tests and bone marrow infiltration were independent prognostic factors of PFS. Only a positive Coombs test tended to be associated with lower OS rates. There were no statistically significant differences in hematologic toxicity between the two groups (P=0.299). Non-hematological toxicity in the CHOP-T group, such as diarrhea, peripheral neuropathy, and somnolence/fatigue, was significantly higher than in the CHOP group (P=0.017). The present study showed that the CHOP-T regimen was more effective than the CHOP regimen in improving OS and CR rates, but non-hematological toxicities were higher. Severity of diarrhea, peripheral neuropathy, and somnolence/fatigue was significantly associated with thalidomide and no efficient precautions were observed.

Keywords: Angioimmunoblastic T-cell lymphoma, efficacy, survival analysis, adverse events

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a rare form of non-Hodgkin's lymphoma that originates in follicular helper Tcells (TFH) [1]. AITL is an uncommon malignancy, accounting for 1%-2% of peripheral T-cell lymphomas (PTCL) [2]. It displays an aggressive course with fever, rashes, generalized lymphadenopathy, splenomegaly, and other systemic symptoms. It is more associated with immune dysfunction. From a histological point of view, a French group reported that Epstein-Barr virus-positive T-cell blasts were evident in 77% of cases and 93% of cases were found to have an expansion of follicular dendritic cells [3]. A study from Italy demonstrated prominent vascular proliferation in AITL and overexpression of vascular endothelial growth factor (VEGF), both in lymphoma and in endothelial cells [4]. Two large multicenter studies showed that more than 80% of patients had Ann Arbor stage III or IV disease, while 14% presented with an International Prognostic Index (IPI) of 0 or 1 and 72% had B symptoms [5, 6]. There is no consensus regarding prognostic factors associated with the disease. Prognostic factors reported in the literature include Eastern Cooperative Oncology Group Performance Status (ECOG) scores, Ann Arbor stage, hemoglobin levels, and genetic abnormalities. Other reports have suggested that IPI scores do not apply to AITL [7]. Several retrospective studies have been conducted, reporting 5-year overall survival (OS) rates of approxi-

mately 30% with anthracycline-containing regimens [8-10]. Intensive chemotherapy does not improve OS rates due to adverse events (AEs) [5]. Autologous stem cell transplantation (ASCT) can improve the prognosis of young patients with complete remission, but it is not suitable for elderly patients [11]. Thalidomide and lenalidomide are immunomodulatory drugs. They have potent anti-inflammatory and antiangiogenic effects [12, 13]. In recent years, scattered case reports have shown benefits of lenalidomide use in AITL, but lenalidomide-associated myelosuppression and high costs have limited its use [14, 15]. AEs of thalidomide include drowsiness, fatigue, constipation, peripheral neuropathy (PN), venous thrombus embolism (VTE), rashes, dry mouth, hand tremors, irregular menstruation, lower extremity edema, bradycardia, and neutropenia. These have been mainly reported in the studies of multiple myeloma (MM). However, outcomes of a thalidomide combination regimen in AITL have not yet been reported, but will be explored in the present research.

Materials and methods

Patient selection

Ethical approval (no. 2016MEC069) was given by the Medical Ethics Committee of the Fourth Hospital of Hebei Medical University, Shijiazhuang, PR China. Clinical data of 48 primary AITL patients, aged 35 and above, consecutively enrolled from the Fourth Hospital of Hebei Medical University, between September 1 2009 and December 31, 2014, were collected. Diagnosis of AITL was based on 2008 World Health Organization classification criteria [16]. Data collection was from retrospective reviews of medical records. Patients have reported no plans to conceive since receiving their diagnosis. Examination of the 48 patients included a complete clinical history, physical examination, complete blood count, renal and liver function levels, serum albumin, lactate dehydrogenase (LDH), β2-microglobulin, Coombs test, bone marrow biopsy, and computerized tomography (CT) scans of the brain, chest, abdomen, and pelvis. The stage of patient disease was in accordance with the Ann Arbor classification [17]. Performance status was evaluated according to the ECOG scale [18]. Risk stratification was in accordance with IPI and the prognostic index for peripheral T-cell lymphoma (PIT) unspecified was utilized [19, 20].

Treatment and response evaluation

All patients received more than four courses of chemotherapy. For the 31 patients in the cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) group, treatment consisted of cyclophosphamide 750 mg/m^2 intravenous (i.v.), vincristine 1.4 mg/m^2 i.v. and doxorubicin 50 mg/m^2 i.v. on day 1, along with prednisone 50 mg/d per os (PO) on days 1-5, in a 21-day cycle. For the 17 patients in the cyclophosphamide, doxorubicin, vincristine, prednisolone, and thalidomide (CHOP-T) group, treatment consisted of the CHOP regimen combined with thalidomide 100 mg/night PO. Thalidomide was administered from the beginning of chemotherapy until the patient could not tolerate it or until death. If patients failed to achieve complete remission (CR) or partial response (PR) after four cycles of chemotherapy, treatment was adjusted to ifosfamide-containing regimens. However, the use of thalidomide was not adjusted. Patients with CR after completion of eight cycles of CHOP or CHOP-T regimens were not given additional chemotherapy until progression of disease (PD). Patients with stable disease (SD) and PD were suffered another high-dose salvage regimen containing cisplatin or cytarabine or gemcitabine, if possible. Appropriate treatment was given to patients according to chemotherapy-induced AEs experienced, including granulocyte colony-stimulating factor, thrombopoietin, apheresis platelets, and suspended leukocyte-reduced red blood cells. Patients in the CHOP-T group, if platelets were above 50×10^9/l, were given a low molecular weight sodium heparin subcutaneous injection of 4000 IU twice daily during hospitalization and outpatient oral aspirin 75-100 mg/d until the withdrawal of thalidomide. Extracts from rabbit skin inflamed by the vaccinia virus 3 mg/d IV during hospitalization, outpatient oral vitamin B1 30 mg three times a day, and vitamin B12 50 μg three times a day were administered. Prophylactic antiemetic, laxative, and protective agents for gastric mucosa during treatment were also administered. No patients rejected the ASCT transplant. Treatment response was based on computerized tomography scans of the chest, abdomen, and pelvis after every second cycle and every 3-6 months

Table 1. Clinical features of 48 patients and prognostic factors for OS and PFS

Characteristic	CHOP (31)/ CHOP-T (17)	*p*	2-year OS	Univariate *p*	Multivariate *p*	2-year PFS	Univariate *p*	Multivariate *p*
Sex								
Male	15/9	1	44.60%	0.256		35.70%	0.735	
Female	16/8		62.50%			37.50%		
Age								
>60	15/6	0.544	46.40%	0.257		36.40%	0.616	
≤60	16/11		59.30%			37%		
B symptom								
Yes	27/14	0.686	50.70%	0.354		33%	0.217	
No	4/3		71.40%			57.10%		
ECOG score								
≤2	26/11	0.163	61.90%	0.082		37.80%	0.492	
>2	5/6		27.30%			32.70%		
LDH								
Normal	12/10	0.232	81.80%	<0.001	0.436	54.50%	0.001	0.628
High	19/7		29.90%			21%		
β2-microglobulin								
normal	5/4	0.701	55.60%	0.638		44.40%	0.461	
>2.8 mg/l	26/13		53.50%			34.80%		
Serum albumin levels								
≥35 g/l	12/8	0.76	70%	0.026	0.72	50%	0.055	
<35 g/l	19/9		42.10%			26.80%		
Ki67								
High (≥70%)	9/5	1	40.80%	0.344		16.30%	0.103	
Low (<70%)	22/12		58.80%			44.10%		
Coomb's test								
Positive	11/4	0.521	16.70%	<0.001	0.016	0%	<0.001	<0.001
Negative	20/13		69.70%			53.60%		
Bone marrow								
Positive	9/3	0.497	8.30%	<0.001	0.178	0%	<0.001	0.009
Negative	22/14		69%			49%		
Ann Arbor stage								
I/II	4/7	0.036	90.90%	0.005	0.094	54.50%	0.102	
III/IV	27/10		39.80%			31.30%		
IPI								
Low and Low-intermediate	13/9	0.551	90.90%	<0.001	0.755	59.10%	<0.001	0.075
High-intermediate and High	18/8		21.40%			16.90%		
PIT								
Group1/2	14/8	1	81.80%	<0.001	0.473	54.50%	0.001	0.742
Group3/4	17/9		29.60%			20.80%		

PFS progression-free survival, *OS* overall survival, *ECOG* Eastern Cooperative Oncology Group, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisolone, *CHOP-T* cyclophosphamide, doxorubicin, vincristine, prednisolone, and thalidomide, *IPI* international prognostic index, *PIT* prognostic index for peripheral T cell lymphoma.

in the first 2 years following therapy. Response to treatment, including CR, PR, SD, or PD, was defined according to the 2014 Lugano classification for malignant lymphoma [21]. Four courses of intrathecal methotrexate (10 mg/body) injections, combined with hydrocortisone (10 mg/body) for central nervous system prophylaxis, were administered. These were administered as soon as CR was achieved in cases with serum lactate dehydrogenase levels two times greater than the normal upper limit, bone marrow involvement, skin involvement,

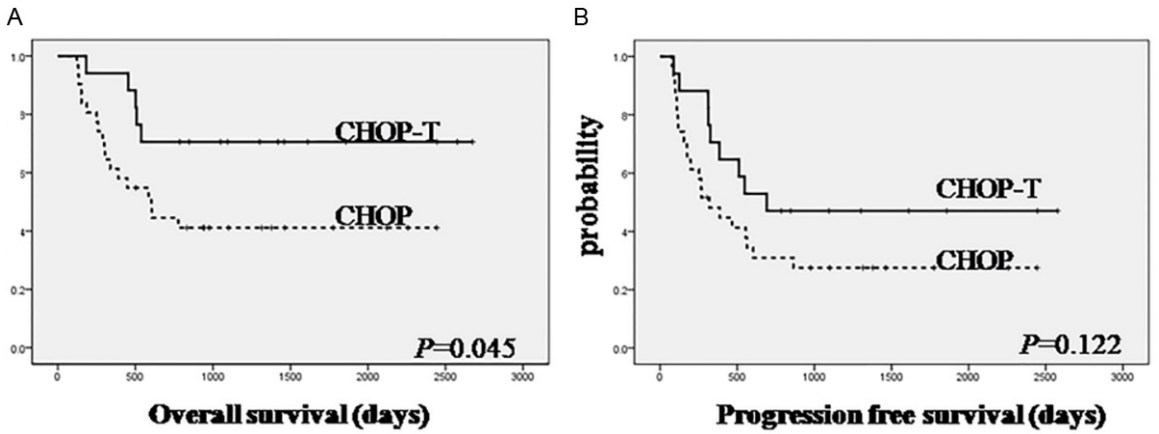

Figure 1. (A) Overall survival (OS) and (B) progression-free survival (PFS) curves according to different regimens. The 2-year OS rate in the CHOP-T group was better than CHOP group (70.6% vs. 44.6%, P=0.045). However, it did not translate into a significantly better PFS (47.1% vs. 31%, P=0.122) rate.

and bone involvement. Primary end points were OS and safety. Secondary endpoints were PFS and CR rates.

AEs evaluations

All AEs during treatment were recorded in accordance with the National Cancer Institute's Common Terminology Criteria for adverse events, version 4.0 (NCI-CTCAE v4.0). Patients in the thalidomide group recorded the highest grade of each AE.

Statistical analysis

Clinical characteristics and AEs were analyzed using Chi-squared tests and Fisher's exact tests, as appropriate, to make comparisons between the two groups. Probabilities of OS and PFS were estimated with the use of the Kaplan-Meier method. Survival curves were constructed using the Kaplan-Meier method with Rothman 95% confidence intervals (CIs) and the groups were compared using the log-rank test. Multivariate analysis for survival was carried out using the Cox regression model. Hazard ratios (HRs) for progression or death were computed first in univariate analysis and then in multivariate analysis for factors with *p*-values less than 0.05. All tests were two-sided. In all analyses, *p*-values <0.05 are considered statistically significant. All statistical analyses were performed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA). OS was defined as the time between the date of the biopsy and date of death. PFS was defined as the time elapsed between the date of the biopsy and date of occurrence of progression, relapse, or death.

Results

Clinical characteristics of AITL patients at diagnosis

Clinical characteristics of the 48 patients are listed in **Table 1**. The median age at diagnosis was 59 (range: 35-75) years. Female patients comprised 50% (24/48). An ECOG score >2 accounted for 22.92% (11/48) of patients. Systemic B symptoms were self-reported in most patients (85.42%, 41/48). A majority, 77.08% (37/48), presented at an advanced disease stage (III/IV). Bone marrow was the most important extranodal involvement (25%, 12/48). Elevated serum LDH (normal range: 120-250 U/l) was found in 54.17% (26/48) of patients. A significant number, 81.25% (39/48), of patients had elevated serum β2-microglobulin levels (normal range: 0.8-2.8 mg/l). Low serum albumin (<35 g/l) and positive Coombs tests accounted for 58.33% (28/48) and 31.25% (15/48), respectively. High Ki67 (≥70%) accounted for 29.17% (14/48). High IPI (>2) and PIT (≥2) score patients accounted for the same proportion (54.17%, 26/48). There were no significant differences in characteristics of the CHOP and CHOP-T groups, except for Ann Arbor stage. Advanced disease stage accounted for 12.9% (4/31) in the CHOP group, compared with 41.18% (7/17) in the CHOP-T group.

Table 2. AEs of grade3/4 were compared between CHOP and CHOP-T

AEs	CHOP (n=190)	CHOP-T (n=122)	HR	95% CI	χ^2	*P*
Leukopenia	32 (16.84%)	27 (22.13%)	0.713	0.402-1.262	1.355	0.3
Thrombopenia	11 (5.79%)	8 (6.56%)	0.876	0.342-2.243	0.077	0.811
Anemia	16 (8.42%)	12 (9.84%)	0.843	0.384-1.849	0.182	0.689
Neutropenia	19 (10%)	16 (13.11%)	0.736	0.363-1.494	0.724	0.463
Total of hematological toxicological	48 (25.26%)	38 (31.15%)	0.747	0.451-1.237	1.288	0.299
Infection	11 (5.79%)	9 (7.38%)	0.772	0.310-1.920	0.312	0.639
Nausea and vomiting	9 (4.74%)	7 (5.74%)	0.817	0.296-2.254	0.153	0.794
Diarrhea	4 (2.11%)	9 (7.38%)	0.27	0.081-0.897	5.171	0.038
Oral mucositis	5 (2.63%)	3 (2.46%)	1.072	0.252-4.569	0.009	1
Nerve headache and peripheral neuropathy (motorius and sensory)	5 (2.63%)	12 (9.84%)	0.248	0.085-0.722	7.485	0.009
Constipation	3 (1.58%)	6 (4.92%)	0.31	0.076-1.264	2.957	0.162
Tetter	3 (1.58%)	5 (4.1%)	0.375	0.088-1.600	1.888	0.27
Hyperglycemia	6 (3.16%)	4 (3.28%)	0.962	0.266-3.481	0.003	1
Hyponatremia and hypokalemia	12 (6.32%)	6 (4.92%)	1.303	0.476-3.570	0.267	0.804
Somnolence/fatigue	5 (2.63%)	13 (10.66%)	0.227	0.079-0.653	8.799	0.005
Edema	1 (0.53%)	3 (2.46%)	0.21	0.022-2.041	2.193	0.303
VTE	3 (1.58%)	0 (0)	1.652	1.510-1.808	1.945	0.283
Total of non-hematological toxicological	33 (17.37%)	36 (29.51%)	0.502	0.292-0.862	6.357	0.017
Total	61 (32.11%)	54 (44.26%)	0.595	0.372-0.952	4.718	0.031

AEs adverse events, *HR* hazard ratio, *CI* confidence interval, χ^2 chi-square test, *VTE* venous thromboembolism, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisolone, *CHOP-T* cyclophosphamide, doxorubicin, vincristine, prednisolone, and thalidomide.

Treatment response and prognostic factors of patients with AITL

The 48 patients underwent a total of 491 cycles of chemotherapy (range: 5-17, median: 9). A total of 312 cycles of the CHOP and CHOP-T regimen were delivered (range: 4-8, median: 7), while other regimens accounted for 179 cycles (range: 0-12, median: 3). In the CHOP group, a total of 190 cycles used the CHOP regimen (range: 4-8, median: 7) and other regimens were used in 122 cycles (range: 0-12, median: 3). In the CHOP-T group, a total of 122 cycles used the CHOP-T regimen (range: 4-8, median: 8) and other regimens were used in 57 cycles (range: 0-8, median: 3). Average treatment time with thalidomide was 846.31 days (range: 180-1173 d, median: 958.5 d). Thirty-one patients (64.6%) achieved CR, 17 patients (54.8%) in the CHOP group and 14 patients (82.4%) in the CHOP-T group. There were no statistically significant differences between the two groups (χ^2=3.634, P=0.068). Two-year OS and PFS rates for all patients were 52.8% and 36.6%, respectively. Two-year OS and PFS rates in the CHOP group were 44.6% and 31%, respectively. Two-year OS and PFS rates in the CHOP-T group were 70.6% and 47.1%, respectively. There were statistically significant differences in OS rates between the two groups (P=0.045), but no statistically significant differences in PFS rates (P=0.122) (**Figure 1**). Seven factors, including elevated serum LDH (P<0.001), low serum albumin (P=0.026), positive Coombs test (P<0.001), bone marrow positive (P<0.001), advanced stage (P=0.005), IPI≥0 (P<0.001), and PIT IPIP<0.001), were identified as poor prognostic factors for OS rates, according to univariate analysis. Multivariate analysis found that only Coombs test was identified as a significant prognostic factor for OS rates (HR 3.644; 95% confidence interval [CI] 1.271-10.442; P=0.016). Elevated serum LDH (P=0.001), positive Coombs test (P<0.001), bone marrow positive (P<0.001), IPI≥3 (P<0.001), and PIT IP(P=0.001) were significantly associated with an unfavorable PFS rates, according to univariate analysis. According to multivariate analysis, positive Coombs test (HR 5.028; 95% CI 2.056-12.298; P<0.001) and bone marrow positive (HR 3.333; 95% CI 1.348-8.239; P=0.009) were identified as independent prognostic factors for PFS rates (**Tables 1**, **2**).

Treatment-related AEs

AEs of grades 3/4 are listed in **Table 2**. Hematological toxicology of the CHOP group was

25.26% (48/190), in contrast to the CHOP-T group with 31.15% (38/122). This difference was not statistically significant (HR 0.747; 95% CI 0.451-1.237; χ^2=1.288 P=0.299). Differences in non-hematological toxicology were statistically significant between the two groups (HR 0.502; 95% CI 0.292-0.862; χ^2=6.357 P=0.017), including diarrhea (HR 0.27; 95% CI 0.081-0.897; χ^2=5.171 P=0.038), peripheral neuropathy (HR 0.248; 95% CI 0.085-0.722; χ^2=7.485 P=0.009), and somnolence/fatigue (HR 0.227; 95% CI 0.079-0.653; χ^2=6.357 P=0.005). It is noteworthy that no thromboembolisms occurred in the CHOP-T group. Eight patients died of lung infections after leucopenia.

Discussion

AITL is a subtype of PTCL, with occurrence rates of 16% in North America, 34.3% in Europe, and 22.4% in Asia [8]. AITL is commonly considered to be a rare subtype of lymphoma, but it seems to be on the rise in recent years. A large-scale study from France has shown that AITL is, by far, the most common PTCL subtype (739 cases, 36%) [3]. The latest statistics from the United States on PTCL show an incidence rate of Asian-American AITL of 16.7%. The median age for AITL in these latest figures was 69 years and more common in males [22]. The course of AITL is aggressive with poor prognosis, diverse clinical manifestations, and atypical histology. Upon diagnosis of AITL, 60%-80% of patients were at stage III/IV. Most patients were found with lymphadenopathy, fevers, bone marrow infiltration, and autoimmune hemolytic anemia [23]. Some reports regarding the prognosis of patients with AITL have been controversial in recent years. Mourad et al. reported that being male and having mediastinal lymphadenopathy and/or anemia were prognostic factors of AITL [5]. Tokunaga et al. found that age, elevated white blood cells, extranodal invasion, anemia, and thrombocytopenia were associated with prognosis [9]. Xu et al. reported that an age above 70 years, advanced-stage disease, and male sex are adverse predictors for OS rates [24]. Kao et al. reported that bone marrow involvement, ECOG>1, IPI>1, and PIT>1 have an adverse impact on OS rates [25]. In the present study, most of the patients were at an advanced stage, had low serum albumin, and had high serum β2-microglobulin. Almost all patients had B symptoms. Patients with high IPI and PIT scores were more common in this study. IPI and PIT scores in invasive lymphoma and PTCL have good prognostic significance [26]. However, the present study showed that IPI>2 and PIT≥2 did not correlate with worsening OS or PFS rates, according to multivariate analysis. In fact, these two integral prediction systems have been controversial in AITL studies. Two large-scale studies of AITL, from Mourad et al. and Federic et al., suggested that IPI was unpredictable as a survival rate system [5, 10]. In contrast, a recent study from Japan by Tokunaga et al. demonstrated that both IPI and PIT are good predictors of prognosis [9]. Many possible factors could have caused these results to differ, such as ethnic differences and diversity of chemotherapy regimens. In conclusion, the role of IPI is controversial in predicting prognosis of AITL and more research is necessary to confirm it. Coombs tests and bone marrow were independent prognostic factors of OS rates. Bone marrow infiltration and positive Coombs test patients showed worse outcomes. AITL patients are often associated with abnormal serum immune parameters. This often causes a variety of clinical symptoms and organ damage, thus it may be associated with poorer prognosis. Present researchers will be conducting a study with immune-related prognostic indicators in a follow-up test. Bone marrow infiltration and abnormal serum immune parameters often lead to a decreased tolerance of chemotherapy. Different chemotherapy regimens have shown different prognostic indicators. The addition of thalidomide helps to overcome common poor prognostic indicators, but further randomized case-control studies are necessary.

Many studies have shown poor prognosis with AITL. In a retrospective study of 1,207 patients with AITL from China, between 1973 to 2010, OS rate probabilities at 2-, 5-, and 10-years were 46.8%, 32.9%, and 21.9%, respectively [24]. This research failed to find any survival rate differences among subgroups diagnosed in the five periods studied (1992-1998, 1999-2001, 2002-2004, 2005-2007, and 2008 to 2010). In other words, there has been no improvement in survival rates for AITL patients over the past two decades in China. The prognosis of patients with AITL in China is the same as in Europe and the United States. The range

of CR rates was from 46% to 60% in the above-mentioned studies, with a 2-year PFS rate of nearly 40% and 2-year OS rate of less than 55%. The efficacy of chemotherapy regimens is often improved by increasing the dose of chemotherapy drugs, intensive chemotherapy, or targeted drug applications. There was no recognized effective chemotherapy regimen found for AITL by a prospective multicenter clinical trial, due to low incidence. Anthracycline-containing regimens, often used as first-line options, include hormones, cytotoxic drugs, and immunomodulators. Usually, patients have a good response to the treatment, but its effects cannot be sustained [10]. Adjusting the intensity of the treatment regimen, including high-dose drugs and/or weakening and strengthening chemotherapy, did not achieve long-term survival in AITL patients. A retrospective study from GELA showed that the five-year OS rate of AITL is 32%-33%. There were no significant differences in OS rates between ACVBP, CHOP, and mBACOD regimens [5]. A similar conclusion was made by a research study in Japan [27]. Several prospective studies have shown that THP-COP 50 mg/m^2 pirarubicin, 750 mg/m^2 cyclophosphamide, 1.4 mg/m^2 vincristine (2.0 mg maximum) on day 1, and 100 mg/body predonisolone on days 1-5, at 3-week intervals, had no further benefit in survival rates, compared with CHOP at 3-week intervals [28, 29]. A total of 17 PTCL patients (AITL, n=12) received biweekly THP-COP when enrolled in a phase II study. The 3-year PFS and OS rates were 57% and 75%, respectively. Biweekly THP-COP may be a safe and promising therapy for patients with a recent diagnosis of AITL [30].

ASCT has been shown to be an effective treatment for patients that are sensitive to chemotherapy agents and have high recurrence rates, according to a recent study from Germany which included 111 patients with PTCL [11]. ASCT is an important means for AITL patients to achieve long survival. However, older patients with AITL are common, usually with immune disorders and higher ECOG scores. Therefore, ASCT is often intolerable. Combination of targeted drugs or immunomodulators is a promising treatment option for patients that cannot tolerate ASCT. AITL cells derived from TFH, a proportion of neoplastic T-cells, are highly variable. Most AITL can be detected in Epstein-Barr virus infections of progenitor B-cells. B-cell disorders play an important role in AITL [13]. Delfau et al. used rituximab combined with a CHOP regimen to treat 25 patients with AITL. The patients received no significant benefits, compared with traditional chemotherapy, due to the high recurrence rate in a short period of time [31]. Chidamide is a novel benzamide type of subtype-selective histone deacetylase inhibitors. Ten relapsed/refractory patients with AITL enrolled in a phase II study in China had higher OR (50%) and CR rates (40%) with chidamide treatment [32]. Some small sample studies and case reports have shown that a combination of clarithromycin or bortezomib may improve CR rates in AITL patients [33-35]. There are also some new drugs that have shown good efficacy and safety, including a CD30-directed antibody-drug conjugate (brentuximab vedotin) and Alisertib (a novel oral Aurora A kinase inhibitor) [36, 37]. However, a large sample of clinical trials and long-term follow-up is needed to confirm their efficacy and safety. To summarize, there is no clear evidence that increasing the dose of chemotherapy drugs, using intensive chemotherapy, or targeted drug applications can significantly improve survival rates of AITL patients. The present study showed that the CHOP group and CHOP-T group had 2-year PFS rates and CR rates in accord with those in previous studies. However, the OS rate of the CHOP-T group was significantly higher than the CHOP group (70.6% vs. 44.6%), compared to previous reports. The CHOP-T regimen may extend the overall survival rate of patients with AITL. Although AITL cannot be cured, at present, we hope for AITL to be controlled like other common chronic diseases and hope that survival rates improve with low toxicity, high efficiency and convenient medications. Many studies have provided molecular and morphological evidence to define that the TFH cell is the cell of origin for AITL. These studies have identified oncogenic pathways of AITL, including the nuclear factor-κB pathway, interleukin-6 signaling, and transforming growth factor β pathway [38, 39]. In a study that reviewed 236 AITL cases, characteristic morphological features that were present in most cases included polymorphic cellular infiltration (100%), arborizing vessels (98%), blast cells (94%), clear cells (69%), and sinus sign (72%) [10]. AITL is also often associated with polyclonal plasmacytosis and polyclonal hypergam-

maglobulinemia [40, 41]. Some of these features may be explained by the properties of neoplastic T-cells, such as TFH cells [42]. Thalidomide is a synthetic glutamic acid derivative with anticancer and anti-inflammatory properties. Many previous reports have indicated that MM, myelodysplastic syndrome, and acute myelocytic leukemia can be treated with thalidomide successfully. In mice splenocytes, Kim et al. found that thalidomide may have an immune modulatory effect by selectively suppressing CD4+ effector T-cell proliferation. This may be one of the mechanisms that thalidomide utilizes to be effective in the treatment of T-cell disease [43]. Scholars have reported that thalidomide has achieved good effects in AITL, although these have mostly been in small samples or case reports. In 2002, Strupp et al. first applied thalidomide to AITL and achieved complete remission [44]. In 2005, Dogan et al. reported that a 78-year-old AITL patient achieved long-term sustained remission with thalidomide [45]. In 2008, Gottardi et al. reported that a refractory case had endured multiple chemotherapy regimens and ASCT. The patient continued oral administration of thalidomide (200 mg/d) for 7 months. Disease received both imaging and biological mitigation for one month and maintenance for 7 months [46].

With regards to thalidomide, although its precise mechanisms accounting for the efficacy in treating AITL remain unclear, its effects include the downregulation of pro-inflammatory cytokines, enhanced CD8+ T-cell responses, alterations in the expression of cell adhesion molecules, and reductions in prostaglandins [47]. Thalidomide can further inhibit the proliferation of vascular endothelial cells in patients. It can also regulate cytokines to enhance Th1-mediated cellular immune function. VEGF is a key factor in angiogenesis and lymphangiogenesis through its activity as a highly specific mitogen for endothelial cells [47]. AILT shows high expression of VEGF on both tumor cells and endothelial cells and is the most prominent vascular component among AITL. In addition, VEGF expression is related to poor prognosis of AITL [48]. Results of a recent randomized trial in non-Hodgkin's lymphoma indicated that thalidomide reduced soluble VEGF levels. Therefore, the VEGF pathway appears to be involved in the effects of thalidomide. Based on these data, the effectiveness of thalidomide treatment may be associated with inhibitory effects of thalidomide on VEGF production. A phase II clinical trial examined the effects of fludarabine and cyclophosphamide, followed by thalidomide for AITL [13]. Poor outcomes were observed in this trial, with patient early high mortality rates appearing to be a result of the fludarabine-associated hematological toxicity. There have been no long-term follow-ups examining survival rates regarding to thalidomide combined chemotherapy. Combining the above-mentioned studies and results of the present study, the CHOP-T regimen has the potential to be a new regimen to improve the OS rates of AITL. However, an increase in chemotherapy toxicity is also a concern.

Thalidomide was originally used to alleviate morning sickness in pregnant women but was banned due to severe adverse effects [49]. We informed patients that strict contraceptive use was essential during treatment. Retrospective analysis of AEs that may have caused the termination of medication use or that were life-threatening included somnolence/fatigue, constipation, peripheral neuropathy, and VTE. A study showed that incidence of AEs with thalidomide was related to the dose [50]. With a daily dose of less than 200 mg, the incidence of AEs is lower. The present study showed that somnolence/fatigue occurred in almost all patients, but that incidence of severe reactions was approximately 10%. To reduce discomfort during the day, it was recommended that patients take their medication at bedtime. It was established that 100 mg/night could be tolerated. More than 80% of patients reported thalidomide-induced PN, including numbness of the extremities, tingling, stiff fingers, and unsteady walking. These side effects were more obvious the longer that patient took the medication. With long-term use of thalidomide, for more than 6 months, the incidence of PN was significantly increased [50]. Tramadol and carbamazepine had a good analgesic effect for intense tingling sensations. In this study, grade 3/4 PN was significantly increased in the CHOP-T group, compared to the CHOP group. This may be related to the long recovery times of neurotoxins and other neurotoxic drugs (vincristine) in chemotherapy regimens. There were no apparent effects from neurotrophic drugs, such as mecobalamin. Constipation was the most common AE of thalidomide use, especially in elderly

patients or patients with previous history of constipation. Thalidomide usually is not discontinued because of constipation. In this study, it was recommended that patients take thalidomide with laxatives. Therefore, compared to the CHOP group, there was no significant difference in constipation, but diarrhea was significantly increased. This may be associated with the neurotoxicity of thalidomide. VTE is a troublesome and dangerous side effect that can lead to pulmonary embolisms. Patients often present with swelling in the side of a limb. Vascular ultrasounds can aid in the diagnosis. Incidence of VTE with thalidomide alone was increased at least 2.1-fold and VTE increased 3.1-fold (25%) when combined with high doses of dexamethasone [51, 52]. The highest incidence of VTE was in the first three-six months of thalidomide treatment. Low-molecular-weight heparin (LMWH), low-dose warfarin, and aspirin are antithrombotic agents that reduced VTE incidence to 5-8% of patients treated with thalidomide [52]. This is particularly evident in the treatment of myeloma. However, present clinical experience shows that incidence of thrombosis in Chinese patients was significantly lower than in Europe and US, possibly related to ethnic differences. Application of anticoagulant therapies and effective chemotherapies to improve the symptoms may be an important means to avoid VTE, confirmed by the present study. Results suggest that subcutaneous LMWH sequential oral aspirin can effectively prevent VTE in AITL patients with thrombosis. In this study, it was not found that VTE incidence rates correlate with different treatment doses and times. This may need further follow-up.

In summary, AITL patients with positive Coombs tests and bone marrow infiltration had high recurrence rates. A positive Coombs test seems to be more effective in assessing the prognosis of AITL. AITL treated with CHOP-based chemotherapy is ineffective. For patients that cannot tolerate ASCT, dose adjustments in chemotherapy regimens and intensive chemotherapy regimens are not significantly more effective than the CHOP regimen. However, the CHOP-T regimen, which is low in costs and is easily available, has the potential to improve prognosis of AITL. A high CR rate and long OS rate often indicates a higher PFS rate, but the present study did not yield a high PFS rate due to higher recurrence rates. Traditional chemotherapy for AITL patients often results in high drug resistance, followed by a bad prognosis. The present study shows that the addition of thalidomide may reduce the possibility of chemotherapeutic drug resistance and improve the effects of chemotherapy drugs, while delaying the progression of the disease, prolonging the survival time of patients with cancer, and further prolonging overall survival rates. However, the OS rate, especially the PFS rate, of AITL patients seems to be further improved by adjusting the chemotherapy regimen. Thus, the combination of better chemotherapeutic agents containing thalidomide is worth consideration. AITL incidence is low, so the number of cases in this study was small. This was a retrospective observation, thus the second-line of treatment was not uniform. Therefore, there is a need for a large-prospective studies in confirming present findings. Thalidomide at a dose of 100 mg/night has been recommended for use in treatment and maintenance. At the same time, patients should be protected from non-hematological toxicities, including diarrhea, peripheral neuropathy, and somnolence/fatigue. Laxatives and LMWH sequential oral aspirin can be added to prevent constipation and VTE, respectively. The effects of neurotrophic drugs remain to be seen. A thalidomide-containing regimen, primarily a CHOP-T regimen, is a low-risk, efficient, and convenient treatment for AITL.

Disclosure of conflict of interest

None.

Abbreviations

CHOP-T, cyclophosphamide, doxorubicin, vincristine, prednisolone and thalidomide; AITL, angioimmunoblastic T-cell lymphoma; OS, overall survival; PFS, progression-free survival; CR, complete remission; NHL, non-Hodgkin's lymphoma; PTCL, peripheral T-cell lymphomas; TFH, follicular helper T cells; VEGF, vascular endothelial growth factor; IPI, International Prognostic Index; ECOG, Eastern Cooperative Oncology Group Performance Status; AEs, adverse events; ASCT, Autologous stem cell transplantation; PN, peripheral neuropathy; VTE, venous thrombus embolism; MM, multiple myeloma; WHO, World Health Organization; LDH, lactate dehydrogenase; PIT, prognostic index T-cell lymphoma; i.v., intravenous; PO, per os; PR, partial response; PD, progression disease; SD, stable disease; NCI-CTCAE v4.0, National Cancer Institute's Common Termin-

ology Criteria for adverse events version 4.0; Cis, confidence intervals; HRs, Hazard ratios; GELA, Groupe d'Etude des Lymphomes de l'Adulte; THP-COP, pirarubicin, cyclophosphamide, vincristine, predonisolone; LMWH, Low molecular weight heparin.

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