Ann Hematol (2010) 89:331–339
DOI 10.1007/s00277-009-0895-3

REVIEW ARTICLE

T-cell large granular lymphocyte leukemia: an Asian perspective

Yok-Lam Kwong · Wing-Yan Au · Anskar Y. H. Leung · Eric W. C. Tse

Received: 31 August 2009 / Accepted: 22 December 2009 / Published online: 19 January 2010

Abstract To characterize T-cell large granular leukemia in Asia, 22 Chinese patients from a single institute were reported, together with an analysis of 88 Asian and 272 Western patients identified from the literature. In our cohort, anemia due to pure red cell aplasia (PRCA) occurred in 15/22 (68%) of cases, being the most common indication for treatment. Neutropenia was only found in 8/22 (36%) cases, and recurrent infections, the most important clinical problem in Western patients, were not observed. None of our cases presented with rheumatoid arthritis. These clinical features were consistently observed when compared with the 88 other Asian patients. Combined data from our cohort and other Asian cases showed that Asian patients, compared with Western patients, had more frequent anemia (66/110, 60% versus 113/240, 47%; $p=0.044$), attributable to a much higher incidence of PRCA (52/110, 47% versus 6/143, 4%; $p<0.001$). However, Western patients presented more frequently than Asian patients with neutropenia (146/235, 62% versus 33/110, 30%; $p<0.001$) and splenomegaly (99/246, 40% versus 16/110, 15%; $p<0.001$). Notably, Western patients were about eight to ten times more likely than Asian patients to have rheumatoid arthritis (73/272, 27% versus 4/106, 4%; $p<0.001$) and recurrent infections (81/272, 30% versus 3/107, 3%; $p<0.001$). These clinicopathologic differences have important implications on disease pathogenesis and treatment.

Keywords T-cell large granular lymphocyte leukemia · Pure red cell aplasia · Neutropenia · Rheumatoid arthritis · Splenomegaly

Introduction

T-cell large granular lymphocyte (T-LGL) leukemia is a rare chronic lymphoproliferative disorder, characterized by a $CD2^+CD3^+CD4^-CD8^+$ large granular lymphocytosis ($>2\times10^9$/L) [1]. The T-cell receptor (TCR) gene is clonally rearranged, which helps to establish the diagnosis when the large granular lymphocytosis is less than 2×10^9/L [1].

The clinical features of T-LGL leukemia have been described mainly in Western patients [2–4]. Relatively few Asian patients with T-LGL leukemia have been reported [5], so that the behavior of the disease in this population remains unclear. Owing to global population migration, the features and optimal treatment of T-LGL leukemia in Asian patients are becoming important to physicians worldwide.

In order to delineate the clinicopathologic characteristics of T-LGL leukemia in Asia, a cohort of Chinese patients seen at a single center was studied. Asian patients with T-LGL leukemia were also identified from a literature search and reviewed. The combined results were then compared and contrasted with those of Western patients, so as to define similarities and differences of T-LGL leukemia in these two populations.

Electronic supplementary material The online version of this article (doi:10.1007/s00277-009-0895-3) contains supplementary material, which is available to authorized users.

Y.-L. Kwong · W.-Y. Au · A. Y. H. Leung · E. W. C. Tse
Department of Medicine, University of Hong Kong,
Hong Kong, Special Administrative Region,
People's Republic of China

Y.-L. Kwong (✉)
Department of Medicine, Professorial Block,
Queen Mary Hospital,
Pokfulam Road,
Hong Kong, Special Administrative Region,
People's Republic of China
e-mail: ylkwong@hkucc.hku.hk

Materials and methods

Case definitions T-LGL leukemia was defined according to the World Health Organization (WHO) classification criteria, which stipulated that LGL lymphocytosis should at least be 2×10^9/L, lasting for 6 months or longer [1]. However, it has been proposed that for cases with morphologic and immunophenotypic features typical of T-LGL leukemia, even if the LGL lymphocytosis is less than 2×10^9/L and lasts less than 6 months, the diagnosis can still be made if clonal TCR gene rearrangement is present [3]. Such cases were also included in this study.

Patients All patients with T-LGL leukemia diagnosed consecutively from 1996 to 2009 at Queen Mary Hospital, Hong Kong were examined. There were no exclusion criteria.

Review strategy English articles with the term "large granular lymphocyte leukemia" were searched for in PubMed. All returned articles were screened. As the ethnicities of the patients were rarely, if ever, described in published articles, reports from Western countries were regarded to have described Western patients and those from Asian countries Asian patients. The bibliographies of these articles were also examined in order to ensure that all reported cases were covered. Only cases that fit the WHO diagnostic criteria of T-LGL leukemia were included. Cases described as "large granular lymphocyte leukemia," but were negative for CD3 and showed germline TCR gene, which likely corresponded to neoplastic proliferation of natural killer cells [6], were excluded.

Data analysis For Asian patients, since there were relatively few cases described, all articles from single case reports to patient series were studied. For Western patients, to ensure that representative cases were analyzed, only reports containing at least 20 patients were reviewed. Statistical analyses of data were performed by t test or χ^2 test where appropriate (SPSS, Chicago, IL, USA).

Results

Patients A total of 22 ethnic Chinese (14 males, eight females) patients at a median age of 46.5 (21–78) years were diagnosed with T-LGL leukemia during a 14-year period. Their relevant demographic and clinicopathologic features were shown in Table 1. T-LGL leukemia was the primary hematologic disease in 20 patients. In two patients, T-LGL leukemia developed after an antecedent blood disorder. In case 15, T-LGL leukemia of donor cell origin developed after allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia [7]. In case 16, T-LGL leukemia presented 2 years after successful treatment of idiopathic thrombocytopenia purpura. The most frequent presenting feature was anemia (hemoglobin <10 g/dL; 17/22 cases, 77%). Marrow examination showed pure red cell aplasia (PRCA) in 15 cases (68%). No patient had a previous history of use of erythropoietin. Neutropenia (absolute neutrophil count $<1.5\times10^9$/L) was found in eight cases (36%) and none of the patients presented with infections. Granulocyte colony stimulation factor was not used in any of the cases, so that the low frequency of neutropenia was genuine. LGL lymphocytosis ($>2\times10^9$/L) was found in 14 cases (64%). No patient presented with autoimmune phenomena at the time of diagnosis. Case 3 was the only patient who presented with an aggressive course, characterized by fever, organ infiltration, and adult respiratory distress syndrome. All other patients pursued an indolent clinical course predominated by transfusion-dependent anemia.

Treatment Nineteen patients were given treatment. The treatment indications were anemia (n=15), lymphocytosis (n=2), leucopenia (n=1), and severe systemic illness (n=1). Two patients with LGL lymphocytosis but otherwise normal blood counts have not received any therapy. Before 1999, single-agent treatment with cyclophosphamide, chlorambucil, and cyclosporine was used. No patients treated with cyclophosphamide (n=6) and chlorambucil (n=2) responded. Cyclosporine was used in 15 patients. There were four complete remissions, two partial remissions, and nine non-remissions, giving an overall response rate of 6/15 (40%). Fludarabine, 25 mg/m^2/day×3 days; mitoxantrone, 12 mg/day×1 day; dexamethasone 20 mg/day×5 days (FND; monthly for a planned 6 months) was used in thirteen patients, for a median of six (one to six) courses. The outcome had been briefly described previously [8, 9]. There were eight complete remissions. Five patients showed a partial remission with improvement in cytopenias. At a median follow-up of 88 (12–110) months, four patients were still in complete remission, lasting a median of 90 (39–110) months, without any maintenance medication. Two patients had died of unrelated diseases while still in FND-induced remission.

Outcome There were five deaths. Three cases died from unrelated causes (cerebrovascular accident, bladder cancer, graft-versus-host disease). Two cases died from the leukemia [10].

Asian patients identified from the literature Twenty articles were evaluable based on the availability of clinicopathologic features and treatment outcome. Eighty-eight patients

Table 1 Clinicopathologic features and treatment outcome of 22 Chinese patients with T-cell large granular lymphocyte leukemia

	Sex/ age	Blood counts				Presentation	Comorbidities	Treatment			Current status	Molecular	Follow-up (months)
		Hb	ANC	LGL	Plat			No response	Response (time; months)[a]	outcome			
1	M/44	5.4	4.8	4.6	186	PRCA	HBV	CTX	FND×6 (2)	CR for 1 year; relapsed, NR to CsA, CR after alemtuzumab, on CsA	CR	NR	88+
2	M/78	5.8	0.5	4.8	173	PRCA	DM	-	FND×6 (0)	PR; CR on CsA, no Rx now	CR	NR	100+
3	F/53	12.1	12.0	5.1	34	HS, PN, Fever, ARDS	-	-	FND×6 (0)	CR, no drugs, neuropathy recovered	CR	MR	110+
4	M/54	5.1	1.6	0.9	179	HS, PRCA	HBV	CsA, CTX	FND×3 (28)	PR; relapsed, CR with alemtuzumab, on CsA	CR	NR	98+
5	M/68	6.0	1.4	1.2	195	PRCA	TB, CRF	CsA	FND×1 (35)	CR×1 year; relapsed	.	NR	
									FND×3 (55)	CR×6 months; relapsed	Died of sepsis	MR	37
6	M/50	8.5	1.2	2.1	256	PN, PRCA	-	CsA	FND×6 (44)	PR, neuropathy, CR with CsA	CR	MR	110+
7	M/46	4.7	1.3	2.0	161	HS, PRCA	CRF	CsA	FND×6 (59)	CR	CR	MR	98+
8	M/40	5.0	1.3	1.2	136	HS, PRCA	HBV	CsA, CTX, ATG/ CsA	FND×3 (83)	PR; relapsed while on CsA, CR after alemtuzumab	CR	MR	94+
9	M/52	6.2	1.5	3.9	215	PRCA	DM, TB, CRF	CsA, ATG, CTX, CLB	FND×1 (84)	CR	Died of CVA	NR	12
10	M/71	9.8	1.8	10.2	66	PRCA, S	Bladder CA	-	FND×6 (0)	CR	Died of bladder CA	MR	58
11	F/43	8.9	1.1	7.4	431	PRCA	-	-	FND×6 (0)	CR	CR	NA	63+
12	F/41	8.7	0.8	5.1	490	PRCA, S	-	-	FND×6 (0)	CR	CR	MR	39+
13	M/21	5.3	3.5	14.2	166	HS	Pul HT	CsA, CTX	FND×2 (84)	PR, PR to alemtuzumab	Died of disease	NR	36
14	M/48	6.0	9.8	11.6	360	PRCA	-	CsA, ATG, CTX, CLB,	-	Spontaneous remission for 8 years, relapsed, no Rx	Died of HCC	NA	229
15	M/39	9.9	4.6	18.5	83	GVHD	CML, HSCT	-	-	-	Died of GVHD	NR	10
16	F/47	14.7	8.3	3.7	231	ITP	-	-	CsA (14)	PR on CsA	PR	NR	37+
17	M/76	5.3	4.0	0.8	440	PRCA	IHD	-	CsA (0)	CR	CR	NA	33+
18	M/46	9.1	2.6	0.8	258	PRCA	-	-	CsA (0)	CR	CR	NA	17+
19	F/65	13.3	5.0	5.2	370	-	IHD	-	-	Asymptomatic, no Rx	NR	NA	32+
20	F/84	5.0	4.4	1.5	444	PRCA	-	-	CsA (0)	CR	CR	NA	60+
21	F/40	11.8	1.2	0.5	326	-	-	-	-	Asymptomatic, no Rx	NR	NA	24+
22	F/44	11.5	1.7	1.2	85	S	-	-	CsA (0)	PR	PR	NA	3+

M male, *F* female, *Hb* hemoglobin (g/dL), *ANC* absolute neutrophil count ($\times 10^9$/L), *LGL* large granular lymphocyte count ($\times 10^9$/L), *Plat* platelet count ($\times 10^9$/L), *molecular* molecular response judged by polymerase chain reaction for T-cell receptor gene, *Rx* therapy, *FND* fludarabine, mitoxantrone, dexamethasone, *PRCA* pure red cell aplasia, *HBV* hepatitis B virus, *GVHD* graft-versus-host disease, *ITP* immune thrombocytopenia purpura, *CTX* cyclophosphamide, *CR* complete remission, *NR* non-remission, *PR* partial remisson, *CsA* cyclosporin A, *MR* molecular remission, *DM* diabetes mellitus, *HS* hepatosplenomegaly, *PN* peripheral neuropathy, *S* splenomegaly, *ATG* anti-thymocyte globulin, *ARDS* adult respiratory distress syndrome, *CRF* chronic renal failure, *CLB* chlorambucil, *CA* carcinoma, *NA* not available, *Pul HT* pulmonary hypertension, *CML* chronic myeloid leukemia, *HSCT* hematopoietic stem cell transplantation, *CVA* cerebrovascular accident

[a] Time from presentation

(83 Japanese, 5 Chinese; from Japan, Taiwan, and Hong Kong) were identified (patient details were given in supplemental file 1) [5, 11–29]. These patients and our cases presented at a similar age, with comparable frequencies of anemia, neutropenia, thrombocytopenia, and rheumatoid arthritis. However, Asian patients reported in the literature, when compared with our cases, showed a significantly higher frequency of LGL lymphocytosis (77/88, 88% versus 14/22; 64%, $p=0.008$) and a higher mean LGL count (8.0×10^9/L versus 3.4×10^9/L, $p<0.001$), but lower frequencies of hepatomegaly (4/88, 5% versus 5/22, 23%; $p=0.005$), splenomegaly (8/88, 9% versus 8/17, 36%; $p=0.001$), and PRCA (37/88, 42% versus 15/22, 68%; $p=0.028$; Table 2).

Treatment outcome in Asian patients The treatment outcome was available in 29 patients. A complete remission was achieved in 15/20 patients treated with cyclophosphamide and 4/5 patients treated with cyclosporine. Whether these remissions were durable, associated with molecular remission, and had to be maintained by indefinite treatment was unclear. There were four spontaneous remissions.

Comparison of Asian and Western patients Five Western series comprising 272 patients were identified [2, 30–33], who accounted for approximately 60% of all cases described in the literature [3]. Their clinicopathologic features and treatment outcome were shown in Table 3, in comparison with all 110 Asian patients presented herein. The male:female ratio and presentation age were similar. However, anemia was more frequent in Asian than Western patients (66/110, 60% versus 113/240, 47%; $p=0.025$), attributable to a 12-time increased frequency of PRCA (52/110, 47% versus 6/143, 4%; $p<0.001$). On the other hand, Western patients presented more frequently than Asian patients with neutropenia (146/235, 62% versus 33/110, 30%; $p<0.001$) and splenomegaly (99/246, 40% versus 16/110, 15%; $p<0.001$). Notably, Western patients were about eight to ten times more frequent than Asian patients to have rheumatoid arthritis (73/272, 27% versus 4/106, 4%; $p<0.001$) and recurrent infections (81/272, 30% versus 3/107, 3%; $p<0.001$).

Discussion

In reviewing patients in this study, some assumptions were made that might have limitations. While Asian studies were unlikely to have reported non-Asian patients, it might be possible for Western studies to have reported some Asian patients. However, the significant differences observed between Asian and Western studies suggest that different patient populations were involved. Therefore, if Asian patients had been included in Western studies, they would have been the minority. Because of the small number of Asian patients reported in the literature, we elected to include even single case reports in this study so that a reasonable number of patients could be reviewed. A selection bias toward including T-LGL leukemia patients with complications might therefore be introduced. With these limitations, our study still showed a number of interesting observations.

This study described the largest single-center series of T-LGL leukemia in Chinese patients. T-LGL leukemia is actually a very rare disease. It has been estimated that no more than 450 cases have ever been reported worldwide [34]. Our cohort therefore adds substantially to the understanding of this disorder, particularly in Asian patients.

Our series of Chinese T-LGL leukemia patients showed a number of interesting features. Anemia was the principal presenting problem attributed to PRCA in the majority of cases. On the other hand, neutropenia was rare, so that recurrent infections were hardly a clinical problem. Consequently, our case series has a low mortality, with only two patients dying directly from T-LGL leukemia.

When our cases were compared with other Asian patients reported in the literature, there was an apparent lower frequency and count of LGL lymphocytosis, but a higher frequency of PRCA. These disparities might reflect differences in diagnostic approaches. When patients present with LGL lymphocytosis, the diagnosis of T-LGL leukemia is usually not problematic. However, when patients present with anemia without obvious LGL lymphocytosis, T-LGL leukemia may not be immediately obvious. We routinely performed flow cytometry and analysis for TCR gene rearrangement for patients presenting with unexplained cytopenia(s), which enabled us to detect more subtle cases of T-LGL leukemia. In studies where routine investigation for clonal TCR gene rearrangement was not performed, the diagnosis of T-LGL leukemia would understandably be based on LGL lymphocytosis. Therefore, the difference of LGL levels might be related to diagnostic approaches.

These differences notwithstanding, our cases and other Asian patients showed a very high frequency of PRCA. This complication was originally reported at a high frequency in Japanese T-LGL leukemia patients [5]. Subsequently, PRCA has been observed in both Chinese and Western patients [35–37]. With recognition of the importance of PRCA as a cause of anemia in T-LGL leukemia, increasing numbers of cases were reported worldwide. By 2001, PRCA has been established as a consistent albeit infrequent complication of T-LGL leukemia in Western patients [38]. In fact, T-LGL leukemia is now regarded to surpass all other pathologies as the

Table 2 Clinicopathologic characteristics and outcome of 110 Asian patients with T-large granular lymphocyte leukemia

Parameters	Patients		
	Reported Asian[a]	Current series	*p* value
Sex			
Male	43	14	
Female	45	8	0.215
Age (mean±standard error of the mean, years)	58.3±1.7	52.3±3.2	0.118
Hemoglobin			
Mean±standard error of the mean (g/dL)	9.0±0.4	8.1±0.7	0.236
Low (<10 g/dL)	49	17	0.064
Neutrophil count			
Mean±standard error of the mean ($\times 10^9$/L)	3.4±0.3	4.8±1.0	0.179
Low (<1.5×10^9/L)	25	8	0.466
Large granular lymphocyte count			
Mean±standard error of the mean ($\times 10^9$/L)	8.0±0.8	3.4±0.7	<0.001
High (>2×10^9/L)	77	14	0.008
Platelet count			
Mean±standard error of the mean ($\times 10^9$/L)	265±14	204±28	0.436
Low (<150×10^9/L)	13	5	0.367
Hepatomegaly			
Present	4	5	
Absent	84	17	0.005
Splenomegaly			
Present	8	8	
Absent	80	14	0.001
Pure red cell aplasia			
Present	37	15	
Absent	51	7	0.028
Rheumatoid arthritis			
Present	4	0	
Absent	84	22	0.308
Autoimmune phenomena			
Autoimmune hemolysis	1	0	
Autoimmune thyroiditis	1	0	
Bechet disease	1	0	
Aplastic anemia	1	0	
Immune thrombocytopenia purpura	0	1	
Other associated conditions			
Infection as presentation	3	0	
Acute myeloid leukemia	1	0	
Autologous hematopoietic stem cell transplantation	1	0	
Renal allografting	1	0	
Parvovirus B19 infection	1	0	
Allogeneic hematopoietic stem cell transplantation	0	1	
T-cell receptor gene rearrangement			
Clonal rearrangement	70	20	
Non-clonal rearrangement	6	2	
Not reported	11		
Treatment outcome			
Cyclophosphamide-induced remission	15/20	0/6	

Table 2 (continued)

Parameters	Patients		
	Reported Asian[a]	Current series	*p* value
Cyclosporine-induced remission	4/5	4/14	
Fludarabine-induced remission	0	8/13	
Remission induced by other agents	0	0	
Spontaneous remission	4	0	

[a] The results do not always add up to the total number of patients because some data may be missing from the articles reviewed

commonest cause of PRCA [3, 38]. The high frequency of PRCA in our cases (68%) and other Asian patients (42%) is in sharp contrast to the very low frequency of PRCA at 4% in the Western patients reviewed here. The rarity of PRCA was not due to under-reporting, as in a recent Western series where this complication was purposefully looked for, the incidence was only 7% (15/203 cases) [38].

On the other hand, neutropenia was less frequent in Asian patients, as opposed to the high frequency of 62% in Western patients analyzed here and up to 85% in other reviews [4]. Therefore, infections were uncommon in Asian patients, but are the foremost challenge in the treatment of Western patients. Death due to recurrent infections is also uncommon in Asian patients, which is contrary to Western patients, where death due to recurrent infections can be considered a direct consequence of the leukemia.

The observations of these clinical differences may have important implications on disease pathogenesis. Although the cause of neutropenia in T-LGL leukemia remains obscure, it has been postulated that LGL leukemic cells expressed FasL, tumor necrosis factor (TNF)-α and interferon (IFN)-γ [39]. TNF-α and IFN-γ up-regulated Fas expression on myeloid progenitors, which were then induced into apoptosis by the FasL-expressing LGL leukemic cells [39]. Interestingly, these mechanisms overlap with those involved in the neutropenia typically found in rheumatoid arthritis complicated by Felty syndrome. In the latter disease, humoral mediated mechanisms also contribute to shortened neutrophil survival. The shared mechanisms of neutrophil suppression in T-LGL leukemia and Felty syndrome have led to the premise that both disorders might be part of the spectrum of a similar disease process [39]. This proposition may explain the frequent association between T-LGL leukemia and rheumatoid arthritis in Western patients.

In the Western patients reviewed here, splenomegaly occurred in 40% of cases. Although the causes of the splenomegaly were not specified, it could conceivably represent either leukemic infiltration or a Felty syndrome in patients with rheumatoid arthritis. In Asian T-LGL leukemia patients, as splenomegaly happens less frequently, and rheumatoid arthritis is very rare, it can be deduced that Felty syndrome is highly unlikely. This finding may also explain in part why neutropenia is relatively infrequent in Asian T-LGL leukemia patients.

The above observations suggest that different disease mechanisms might be involved in T-LGL leukemia in different populations. T-LGL leukemia has been proposed to arise from chronic activation of T cells due to endogenous or exogenous antigens [40, 41]. The chronic antigenic stimulation then leads to extreme expansion of a clone of $CD8^+$ cytotoxic T-cells [42]. Rheumatoid arthritis and other autoimmune diseases might provide the antigenic stimuli in Western patients [43]. In Asian patients, however, PRCA is the most common complication. LGL leukemic cells with cytotoxic activity against red cell precursors has been postulated to occur in Asian patients [44]. Therefore, it is conceivable that in Asian patients, antigenic stimuli related to erythropoiesis could be involved in T-LGL leukemia associated with PRCA. It is interesting to note that in Western T-LGL leukemia patients, PRCA and rheumatoid arthritis/neutropenia have been observed to be mutually exclusive, again suggesting that they involve different pathogenetic mechanisms [38].

The most important indication for treatment in Western T-LGL leukemia patients is neutropenia. Low-dose cyclophosphamide and methotrexate with or without corticosteroids have been the mainstay of treatment in this population [3]. Amelioration of the neutropenia and suppression of the LGL leukemic clone leads to a high rate of complete remission. However, disease relapse often occurs once treatment is stopped, so that it has been suggested that treatment should continue indefinitely once a response is obtained [3]. Treatment with cyclosporine also improves the cytopenia in T-LGL leukemia, but the leukemic clone is usually unaffected [3, 45]. Cyclosporine treatment is also indefinite [3].

Conversely, the main indication for treatment in Asian patients is PRCA. The efficacy of cyclophosphamide in T-LGL leukemia related PRCA is uncertain [28]. In the Asian patients reviewed here, cyclophosphamide and cyclosporine therapy was effective in some patients. We have previously

Table 3 Comparison of clinicopathologic features and treatment outcome of 110 Asian and 272 Western patients with T-large granular lymphocyte leukemia

Parameters	Asian patients[a]	Western patients[a]	*p* values
Number	110	272	
Gender			
Male	57	125	0.313
Female	53	146	
Anemia (hemoglobin, ≤10 g/dL)			
Present	66	113	0.025
Absent	44	127	
Neutropenia (ANC $\leq 1.5\times10^9$/L)			
Present	33	146	<0.001
Absent	77	89	
LGL lymphocytosis ($\geq 2\times10^9$/L)			
Present	91	133	0.732
Absent	19	31	
Thrombocytopenia ($\leq 150\times10^9$/L)			
Present	18	47	0.218
Absent	92	165	
Hepatomegaly			
Present	9	35	0.109
Absent	101	211	
Splenomegaly			
Present	16	99	<0.001
Absent	94	147	
Pure red cell aplasia			
Present	52	6	<0.001
Absent	58	137	
Rheumatoid arthritis			
Present	4	73	<0.001
Absent	106	199	
Other autoimmune phenomena			
Present	5	5	0.133
Absent	105	267	
Recurrent infections			
Present	3	81	<0.001
Absent	107	191	
Treatment outcome			
Cyclophosphamide-induced remission	15/26	4/23	
Cyclosporine-induced remission	8/19	11/30	
Fludarabine-induced remission	8/13	0	
Remission induced by other agents	0	1/10	
Spontaneous remission	4	1	

[a] The results do not always add up to the total number of patients, because some data may be missing from the articles reviewed

reported that the purine analogue fludarabine together with mitoxantrone and dexamethasone resulted in high remission rates in Chinese T-LGL leukemia patients [9]. Updated results presented here showed that complete remission was maintained in five of 13 fludarabine-treated patients for a median follow-up exceeding 4 years. The advantages of this approach include a finite duration of treatment and the obviation of maintenance therapy. Fludarabine was combined with mitoxantrone and dexamethasone as it is less active as a single agent than in combination regimens. Furthermore, fludarabine as a single agent had been reported to only improve the cytopenias in T-LGL leukemia without eradicating the leukemic clone [46] and fludarabine combined with cyclophosphamide only induced partial remissions in Western T-LGL leukemia patients [32]. Fludarabine combination regimens offers the possibility of a durable remission without maintenance, as opposed to the daunting prospect of indefinite treatment with cyclophosphamide, methotrexate, and cyclosporine.

Finally, the monoclonal anti-CD52 antibody alemtuzumab has also been used in T-LGL leukemia with variable success [31, 47, 48]. It remains to be determined if further

clarification of the pathogenetic pathways in different patient populations might enable these different therapeutic approaches to be used more rationally.

References

1. Chan WC, Foucar K, Morice WG, Catovsky D (2008) T-cell large granular lymphocyte leukaemia. In: Swerdlow SH, Campo H, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds) WHO classification of tumours of haematopoietic and lymphoid tissues. International Agency of Research On Cancer, Lyon, pp 272–273
2. Loughran TP Jr (1993) Clonal diseases of large granular lymphocytes. Blood 82:1–14
3. Sokol L, Loughran TP Jr (2006) Large granular lymphocyte leukemia. Oncologist 11:263–273
4. Rose MG, Berliner N (2004) T-cell large granular lymphocyte leukemia and related disorders. Oncologist 9:247–258
5. Oshimi K, Yamada O, Kaneko T, Nishinarita S, Iizuka Y, Urabe A, Inamori T, Asano S, Takahashi S, Hattori M, Naohara T, Ohira Y, Tigawa A, Masuda Y, Okuda Y, Furusawa S, Sakamoto S, Omine M, Mori M, Tatsumi E, Mizoguchi H (1993) Laboratory findings and clinical courses of 33 patients with granular lymphocyte-proliferative disorders. Leukemia 7:782–788
6. Chan JK, Wong KF, Jaffe ES, Ralfkiaer E (2001) Aggressive NK-cell leukemia. In: Jaffe ES, Harris NL, Stein H, Vardiman JW (eds) Tumours of haematopoietic and lymphoid tissues. World Health Organization Classification of Tumours. IARC Press, Lyon, pp 198–200
7. Au WY, Lam CC, Lie AK, Pang A, Kwong YL (2003) T-cell large granular lymphocyte leukemia of donor origin after allogeneic bone marrow transplantation. Am J Clin Pathol 120:626–630
8. Ma SY, Au WY, Chim CS, Lie AK, Lam CC, Tse E, Leung AY, Liang R, Kwong YL (2004) Fludarabine, mitoxantrone and dexamethasone in the treatment of indolent B- and T-cell lymphoid malignancies in Chinese patients. Br J Haematol 124:754–761
9. Tse E, Chan JC, Pang A, Au WY, Leung AY, Lam CC, Kwong YL (2007) Fludarabine, mitoxantrone and dexamethasone as first-line treatment for T-cell large granular lymphocyte leukemia. Leukemia 21:2225–2226
10. Hwang YY, Leung AY, Ng IO, Chan GS, Chan KW, Tse E, Kwong YL (2009) Protein-losing enteropathy due to T-cell large granular lymphocyte leukemia. J Clin Oncol 27:2097–2098
11. Oshimi K, Hoshino S, Takahashi M, Akahoshi M, Saito H, Kobayashi Y, Hirai H, Takaku F, Yahagi N, Oshimi Y et al (1988) Ti (WT31)-negative, CD3-positive, large granular lymphocyte leukemia with nonspecific cytotoxicity. Blood 71:923–931
12. Ohno Y, Amakawa R, Fukuhara S, Huang CR, Kamesaki H, Amano H, Imanaka T, Takahashi Y, Arita Y, Uchiyama T, Kita K, Miwa H (1989) Acute transformation of chronic large granular lymphocyte leukemia associated with additional chromosome abnormality. Cancer 64:63–67
13. Morikawa K, Oseko F, Hara J, Kobayashi S, Nakano A, Morikawa S (1990) Functional analysis of clonally expanded CD8, TCR gamma delta T cells in a patient with chronic T-gamma lymphoproliferative disease. Leuk Res 14:581–592
14. Kwong YL, Wong KF, Chan LC, Liang RH, Chan JK, Lin CK, Chan TK (1995) Large granular lymphocyte leukemia. A study of nine cases in a Chinese population. Am J Clin Pathol 103:76–81
15. Masuda M, Arai Y, Nishina H, Fuchinoue S, Mizoguchi H (1998) Large granular lymphocyte leukemia with pure red cell aplasia in a renal transplant recipient. Am J Hematol 57:72–76
16. Akashi K, Shibuya T, Nakamura M, Oogami A, Harada M, Niho Y (1998) Large granular lymphocytic leukaemia with a mixed T-cell/B-cell phenotype. Br J Haematol 100:291–294
17. Takeuchi M, Tamaoki A, Soda R, Takahashi K (1999) Spontaneous remission of large granular lymphocyte T cell leukemia. Leukemia 13:313–314
18. Saitoh T, Karasawa M, Sakuraya M, Norio N, Junko T, Shirakawa K, Matsushima T, Tsukamoto N, Nojima Y, Murakami H (2000) Improvement of extrathymic T cell type of large granular lymphocyte (LGL) leukemia by cyclosporin A: the serum level of Fas ligand is a marker of LGL leukemia activity. Eur J Haematol 65:272–275
19. Kondo H, Mori A, Watanabe J, Takada J, Takahashi Y, Iwasaki H (2001) Pure red cell aplasia associated with parvovirus B19 infection in T-large granular lymphocyte leukemia. Leuk Lymphoma 42:1439–1443
20. Matsuo Y, Drexler HG, Takeuchi M, Tanaka M, Orita K (2002) Establishment of the T-cell large granular lymphocyte leukemia cell line MOTN-1 carrying natural killer-cell antigens. Leuk Res 26:873–879
21. Lee PS, Hwang WS (2002) Pathologic quiz case: chronic anemia with red cell aplasia and lymphocytosis in a middle-aged man. T-cell large granular lymphocyte leukemia. Arch Pathol Lab Med 126:1549–1550
22. Karasawa M, Mitsui T, Isoda A, Tsumita Y, Irisawa H, Yokohama A, Handa H, Matsushima T, Tsukamoto N, Murakami H, Nojima Y (2003) TCR Vbeta repertoire analysis in CD56+ CD16(dim/-) T-cell large granular lymphocyte leukaemia: association with CD4 single and CD4/CD8 double positive phenotypes. Br J Haematol 123:613–620
23. Wong KF, Yip SF, So CC, Lau GT, Yeung YM (2003) Cytomegalovirus infection associated with clonal proliferation of T-cell large granular lymphocytes: causal or casual? Cancer Genet Cytogenet 142:77–79
24. Kato N, Tamura A, Yamanaka Y, Tanimura S, Aikawa K, Morikawa R (2004) CD3+ TCRgammadelta+CD4+ CD8- T-cell large granular lymphocyte leukaemia showing skin infiltrations. Br J Dermatol 150:382–384
25. Narumi H, Kojima K, Matsuo Y, Shikata H, Sekiya K, Niiya T, Bando S, Niiya H, Azuma T, Yakushijin Y, Sakai I, Yasukawa M, Fujita S (2004) T-cell large granular lymphocytic leukemia occurring after autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 33:99–101
26. Shichishima T, Kawaguchi M, Ono N, Oshimi K, Nakamura N, Maruyama Y (2004) Gammadelta T-cell large granular lymphocyte (LGL) leukemia with spontaneous remission. Am J Hematol 75:168–172
27. Tanaka Y, Matsui K, Yamashita K, Matsuda K, Shinohara K, Matsutani A (2006) T-gamma delta large granular lymphocyte leukemia preceded by pure red cell aplasia and complicated with hemophagocytic syndrome caused by Epstein-Barr virus infection. Intern Med 45:631–635
28. Yamada O, Mizoguchi H, Oshimi K (1997) Cyclophosphamide therapy for pure red cell aplasia associated with granular lymphocyte-proliferative disorders. Br J Haematol 97:392–399
29. Kawahara S, Sasaki M, Isobe Y, Ando J, Noguchi M, Koike M, Hirano T, Oshimi K, Sugimoto K (2009) Clinical analysis of 52 patients with granular lymphocyte proliferative disorder (GLPD) showed frequent anemia in indolent T-cell GLPD in Japan. Eur J Haematol 82:308–314
30. Dhodapkar MV, Li CY, Lust JA, Tefferi A, Phyliky RL (1994) Clinical spectrum of clonal proliferations of T-large granular

lymphocytes: a T-cell clonopathy of undetermined significance? Blood 84:1620–1627
31. Osuji N, Matutes E, Tjonnfjord G, Grech H, Del Giudice I, Wotherspoon A, Swansbury JG, Catovsky D (2006) T-cell large granular lymphocyte leukemia: A report on the treatment of 29 patients and a review of the literature. Cancer 107:570–578
32. Aribi A, Huh Y, Keating M, O'brien S, Ferrajoli A, Faderl S, Wierda W, Kantarjian H, Ravandi F (2007) T-cell large granular lymphocytic (T-LGL) leukemia: experience in a single institution over 8 years. Leuk Res 31:939–945
33. Bourgault-Rouxel AS, Loughran TP Jr, Zambello R, Epling-Burnette PK, Semenzato G, Donadieu J, Amiot L, Fest T, Lamy T (2008) Clinical spectrum of gammadelta+T cell LGL leukemia: analysis of 20 cases. Leuk Res 32:45–48
34. Lamy T, Loughran TP Jr (2003) Clinical features of large granular lymphocyte leukemia. Semin Hematol 40:185–195
35. Kwong YL, Wong KF, Liang RH, Chu YC, Chan LC, Chan TK (1996) Pure red cell aplasia: clinical features and treatment results in 16 cases. Ann Hematol 72:137–140
36. Lacy MQ, Kurtin PJ, Tefferi A (1996) Pure red cell aplasia: association with large granular lymphocyte leukemia and the prognostic value of cytogenetic abnormalities. Blood 87:3000–3006
37. Kwong YL, Wong KF (1998) Association of pure red cell aplasia with T large granular lymphocyte leukaemia. J Clin Pathol 51:672–675
38. Go RS, Li CY, Tefferi A, Phyliky RL (2001) Acquired pure red cell aplasia associated with lymphoproliferative disease of granular T lymphocytes. Blood 98:483–485
39. Burks EJ, Loughran TP Jr (2006) Pathogenesis of neutropenia in large granular lymphocyte leukemia and Felty syndrome. Blood Rev 20:245–266
40. Epling-Burnette PK, Loughran TP Jr (2003) Survival signals in leukemic large granular lymphocytes. Semin Hematol 40:213–220
41. Zambello R, Trentin L, Facco M, Cerutti A, Sancetta R, Milani A, Raimondi R, Tassinari C, Agostini C, Semenzato G (1995) Analysis of the T cell receptor in the lymphoproliferative disease of granular lymphocytes: superantigen activation of clonal CD3+ granular lymphocytes. Cancer Res 55:6140–6145
42. Wlodarski MW, O'Keefe C, Howe EC, Risitano AM, Rodriguez A, Warshawsky I, Loughran TP Jr, Maciejewski JP (2005) Pathologic clonal cytotoxic T-cell responses: nonrandom nature of the T-cell-receptor restriction in large granular lymphocyte leukemia. Blood 106:2769–2780
43. O'Malley DP (2007) T-cell large granular leukemia and related proliferations. Am J Clin Pathol 127:850–859
44. Mori KL, Furukawa H, Hayashi K, Sugimoto KJ, Oshimi K (2003) Pure red cell aplasia associated with expansion of CD3+ CD8+ granular lymphocytes expressing cytotoxicity against HLA-E+cells. Br J Haematol 123:147–153
45. Sood R, Stewart CC, Aplan PD, Murai H, Ward P, Barcos M, Baer MR (1998) Neutropenia associated with T-cell large granular lymphocyte leukemia: long-term response to cyclosporine therapy despite persistence of abnormal cells. Blood 91:3372–3378
46. Sternberg A, Eagleton H, Pillai N, Leyden K, Turner S, Pearson D, Littlewood D, Hatton C (2003) Neutropenia and anaemia associated with T-cell large granular lymphocyte leukaemia responds to fludarabine with minimal toxicity. Br J Haematol 120:699–701
47. Au WY, Lam CC, Chim CS, Pang AW, Kwong YL (2005) Alemtuzumab induced complete remission of therapy-resistant pure red cell aplasia. Leuk Res 29:1213–1215
48. Schützinger C, Gaiger A, Thalhammer R, Vesely M, Fritsche-Polanz R, Schwarzinger I, Ohler L, Simonitsch-Klupp I, Reinhard F, Jäger U (2005) Remission of pure red cell aplasia in T-cell receptor gammadelta-large granular lymphocyte leukemia after therapy with low-dose alemtuzumab. Leukemia 19:2005–2008