T-cell large granular lymphocyte leukemia: an Asian perspective

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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 (>2×10⁹/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 2×10⁹/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.
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 $2 \times 10^9/L$, 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 $2 \times 10^9/L$ 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 $\chi^2$ 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 clinico-pathologic 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 $<1.5 \times 10^9/L$) 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 ($>2 \times 10^9/L$) 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 ($n=2$), leukopenia ($n=1$), 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 clinico-pathologic features and treatment outcome. Eighty-eight patients
| Sex/age | Blood counts | Presentation | Comorbidities | Treatment | Response (time; months)$^a$ | outcome | Current status | Molecular follow-up (months) |
|---------|--------------|--------------|---------------|-----------|--------------------------|---------|----------------|----------------------------|
| Hb      | ANC          | LGL          | Plat          |           |                          |         |                |                            |
| 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     | 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 | 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, Bladder CA, - | FND×1 (84) CR | Died of CVA | NR            | 12                         |
| 10      | M/71         | 9.8          | 1.8           | 10.2      | 66 PRCA, S              | -       | FND×6 (0) CR | Died of bladder CA | CR     | NA            | 63                         |
| 11      | F/43         | 8.9          | 1.1           | 7.4       | 431 PRCA                | -       | -              | FND×6 (0) CR | CR     | MR            | 39                         |
| 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 | 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 | 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 | PR     | NA            | 3                         |

M male, F female, Hb hemoglobin (g/dL), ANC absolute neutrophil count (×10⁹/L), LGL large granular lymphocyte count (×10⁹/L), Plat platelet count (×10⁹/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 remission, 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                                      | Reported Asian⁴ | 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 \( \times 10^9/\)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 \( \times 10^9/\)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 \( \times 10^9/\)L)                  | 13              | 5             | 0.367         |
| Hepatomegaly                                    |                 |               |               |
| Present                                         | 4               | 5             | 0.005         |
| Absent                                          | 84              | 17            |               |
| 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           |               |
The 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
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

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

| Parameters                          | Asian patients | Western patients | 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 ≤1.5×10^9/L)       |                |                  |          |
| Present                             | 33             | 146              | <0.001   |
| Absent                              | 77             | 89               |          |
| LGL lymphocytosis (≥2×10^9/L)       |                |                  |          |
| Present                             | 91             | 133              | 0.732    |
| Absent                              | 19             | 31               |          |
| Thrombocytopenia (≤150×10^9/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              |          |

a The results do not always add up to the total number of patients, because some data may be missing from the articles reviewed.
clarification of the pathogenetic pathways in different patient populations might enable these different therapeutic approaches to be used more rationally.

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