Clinical Features and Treatment Outcomes of 81 Patients with Aggressive Type Adult T-cell Leukemia-lymphoma at a Single Institution over a 7-year Period (2006-2012)

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Abstract

Objective  Despite the remarkable advances in chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT), adult T-cell leukemia-lymphoma (ATL) is still associated with a high mortality rate. It is therefore essential to elucidate the current features of ATL.

Methods  We retrospectively analyzed 81 patients with aggressive type ATL at our institution over a 7-year period based on Shimoyama’s diagnostic criteria.

Results  Eighty-one patients with a median age of 67.5 years were classified as having acute (n=47), lymphoma (n=32), or chronic type (n=2) ATL. They were initially treated by either palliative therapy (n=25) or systemic chemotherapy [n=56; cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy (n=25)/vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP) therapy (n=25)/vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP-AMP-VECP) therapy (n=25)]. Subsequent to the initial treatment, HSCT (n=6) was performed for certain patients, thus revealing that two-thirds (n=4) relapsed, and one-third (n=2) survived for 131 days and 203 days, respectively. The relapsed ATL patients were treated with conventional salvage therapy (n=29) or anti-CC chemokine receptor 4 antibody (mogamulizumab) (n=3). The patients treated with mogamulizumab demonstrated complete response (2) and partial response (1) with short duration periods of 82 days, 83 days, and 192 days, respectively.

Among the five long-term survivors (>5 years) who received chemotherapy, most showed a low and intermediate risk according to the ATL prognostic index.

Conclusion  In our study, the overall survival of ATL remains poor due to the advanced age of the patients at diagnosis, a high proportion of patients receiving palliative therapy, and a small proportion of long-term survivors receiving chemotherapy and undergoing HSCT. This study illustrates the current clinical features, treatment strategies, and outcomes in clinical practice.

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Received for publication October 22, 2013; Accepted for publication September 9, 2014

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Key words: adult T-cell leukemia-lymphoma, poor prognosis, a high proportion of palliative therapy, a small proportion of long-term survivors with chemotherapy, a small proportion of hematopoietic stem cell transplantation

Introduction

Adult T-cell leukemia-lymphoma (ATL) is caused by the clonal proliferation of human T-cell leukemia virus type 1 (HTLV-1)-infected CD4 T cells (1, 2). In 1977, Uchiyama et al. were the first to report the clinical features of ATL (1). Approximately 2-5% of HTLV-1 carriers develop ATL after a latent period that can last for decades, although the mechanism underlying leukemogenesis has not yet been clarified (3).

In 1991, Shimoyama’s criteria, which are based on clinical features and prognostic factors, classified ATL into 4 subtypes: acute, lymphoma, chronic, and smoldering type ATL (4). The latter 2 subtypes are clinically indolent, for which the treatment strategy involves observation until disease progression (4, 5). In contrast, acute and lymphoma type ATL progresses rapidly, and the outcomes are generally poor within 6-12 months (4).

Previous clinical reports by the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG) have provided guidelines for improving the outcome of ATL in the past 2 decades (6, 7). In 2009, the International Consensus Meeting and recent reviews recommended that treatment decisions should be based on the ATL subclassification, prognostic factors at onset, and the response to initial therapy consisting of vincristine, cyclophosphamide, doxorubicin, and prednisone-doxorubicin, vinblastine, and prednisone-vindesine, etoposide, carmustine, and prednisone (VCAP-AMP-VECP) therapy with or without hematopoietic stem cell transplantation (HSCT) for acute and lymphoma type ATL (8-11). HSCT is a promising treatment for ATL patients and shows an overall survival (OS) rate of 30-40% at 3 years after treatment (12-16). Despite the remarkable advances in these treatment modalities, the mortality statistics from the Ministry of Health, Labour and Welfare in Japan show that approximately 1,000 people die annually from ATL—a statistic that has remained unchanged for at least the past decade (17). Therefore, to resolve the discrepancy of remarkable advances in ATL treatment and the unchanged annual death caused by ATL, it may be essential to clarify the clinical features and treatment outcomes of ATL in the real world.

In the present study, we report the clinical characteristics and treatment outcomes of 81 patients with aggressive type ATL who were treated at Miyazaki Prefectural Miyazaki Hospital over the last 7 years.

Materials and Methods

A total of 99 patients were diagnosed with ATL at Miyazaki Prefectural Miyazaki Hospital from January 1, 2006 to December 20, 2012. According to Shimoyama’s criteria for the diagnosis of ATL, which are based on clinical features and prognostic factors (4), we classified 99 ATL patients into acute (47 cases), lymphoma (32 cases), chronic (11 cases), or smoldering type ATL (9 cases). We retrospectively analyzed the incidence, clinical manifestations, treatment, and prognosis of 81 patients with acute (47 cases), lymphoma (32 cases), and chronic type (2 cases) ATL who required treatment. The watch and wait (WW) strategy was used for the remaining patients with chronic type ATL and all patients with smoldering type ATL, according to recommendations from previous reports (4, 5).

At our institution, the treatment strategy for ATL is based on the ATL subclassification; prognostic factors such as age, performance status (PS), hypercalcemia, and infiltrated organ function; presence of complicating infection; and the patient’s decision. Initial systemic treatment, in the absence of disease progression, consists of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy, intensified chemotherapy (VCAP-AMP-VECP therapy or CHOP-VMMV therapy), or palliative therapy.

The systemic chemotherapeutic regimen was as follows: VCAP [vincristine (VCR), 1 mg/m² (maximum 2 mg); cyclophosphamide (CPA), 350 mg/m²; Adriamycin (ADM), 40 mg/m²; and prednisolone (PSL), 40 mg/m²] on day 1, AMP [ADM, 30 mg/m²; ramustine (MCNU), 60 mg/m²; and PSL, 40 mg/m²] on day 8, and VECP [vindesine (VDS), 2.4 mg/m² on day 15; etoposide (ETP), 100 mg/m² on days 15-17; carmustine (CBDCA), 250 mg/m² on day 15; and PSL, 40 mg/m² on days 15-17] on days 15-17 for 1-4 courses due to prolonged and progressive cytopenia (6, 7).

CHOP-VMMV therapy was used as an intensive combination chemotherapy regimen, supported by granulocyte colony-stimulating factor (G-CSF) therapy, and consisted of VCR (1 mg/m²) on day 1, ADM (40 mg/m²) on day 1, CPA (400 mg/m²) on day 1, PSL (40 mg/m²) on days 1 and 8-10, ETP (35 mg/m²) on days 1-8, VDS (2 mg/m²) on day 8, MCNU (50 mg/m²) on day 8, mitoxantrone (MIT) (7 mg/m²) on day 8, and G-CSF (50 mg/m²) on days 9-21 for up to 2-4 courses every 3-4 weeks (18).

CHOP therapy was used as the standard regimen for non-

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Table 1. Baseline Patient Characteristics and Treatment of ATL Patients.

| Characteristic                        | Value                  |
|---------------------------------------|------------------------|
| No. of cases                          | 99 cases               |
| Clinical subtype                      |                        |
| Acute type                            | 47 cases               |
| Lymphoma type                         | 32 cases               |
| Chronic type                          | 11 cases               |
| Smoldering type                       | 9 cases                |
| No. of cases needed to treatment      | 81 cases (acute: 47, lymphoma: 32, chronic: 2) |
| Age (median; range) at onset           | 67.5 [34 – 93]        |
| Sex, male/female                      | 35/46                  |
| Initial treatment                     |                        |
| Palliative therapy                    | 25 cases               |
| Chemotherapy                          | 56 cases               |
| (1)CHOP therapy                       | 25 cases               |
| (2) VCAP-VMP-VECP therapy             | 11 cases               |
| (3) CHOP-VMMV therapy                 | 20 cases               |
| Subsequent treatment                  |                        |
| HSCT                                  | 6 cases (CHOP-VMMV: 3 cases, VCAP-VMP-VECP: 3 cases) |
| For relapse of ATL                    |                        |
| Conventional salvage therapy          | 29 cases (CHASE, DeVIC, ESHAP therapy) |
| Mogamulizumab                          | 3 cases (CHOP: 2 cases, VCAP-VMP-VECP: 1 case) |

Abbreviations: no.: number, HSCT: Hematopoietic stem cell transplantation

Hodgkin lymphoma (NHL) consisting of CPA (750 mg/m²), ADM (50 mg/m²), and VCR (1.4 mg/m²; maximum, 2 mg) on day 1, and PSL (60 mg/m²) on days 1-5 (19) for 1-6 courses.

After the initial treatment regimen, the patients who met the criteria for receiving HSCT were treated with HSCT. The patients with ATL relapse were treated with mogamulizumab or conventional salvage therapy consisting of CHASE therapy, DeVIC therapy, ESHAP therapy, or CHOP therapy.

At our institution, based on the Fukuoka Bone Marrow Transplantation Group (FBMTG) HSCT treatment guidelines (20), the indications for HSCT were: age <60 years, Eastern Cooperative Oncology Group PS of 0-2, adequate liver and kidney function (serum bilirubin <2.0 mg/dL and serum creatinine <2.0 mg/dL), and good disease control [complete response (CR) or partial response (PR)]. Patients younger than 55 years were preconditioned with a myeloablative conditioning regimen (MAC) consisting of total body irradiation (TBI) of 12 gray (Gy) and CPA (120 mg/kg), while those aged 55-60 years were preconditioned with a reduced intensity (RI) conditioning regimen consisting of fludarabin (Flu) (180 mg/m²), busulfan (BU) (6.4 mg/kg), and low dose TBI (2 Gy). Eligible donors included human leukocyte antigen (HLA)-identical related and HLA-identical unrelated donors from the Japan Marrow Donation Program [unrelated bone marrow (UR-BM)] as well as cord blood (CB) from the Japan Cord Blood Bank Network (JCBNW). Prephylaxis for graft-versus-host disease was performed using short-term methotrexate (MTX) plus cyclosporine (CSP) for HSCT using donors from CB and short-term MTX plus tacrolimus (FK 506) for HSCT using donors from UR-BM.

The salvage therapy regimens consisted of CHASE therapy, DeVIC therapy, ESHAP therapy, or CHOP therapy every 3-4 weeks for a total of up to 4 courses in the absence of disease progression, as per regimens described in previous reports (19, 21-23). CHASE therapy consisted of CPA (1,200 mg/m²) (2) on day 3; cytarabine (Ara C) (2 g/m) (2) on days 4 and 5; ETP (100 mg/m) (2) on days 3-5; and dexamethasone (Dex) (40 mg) on days 3-5 (21). DeVIC therapy consisted of Dex (40 mg/d) on days 1-3; ETP (100 mg/m²) on days 1-3; ifosfamide (IFO) (1.5 g/m²) on days 1-3; and CBDA (300 mg/m²) on day 1 (22). ESHAP therapy consisted of ETP (40 mg/m²/d) for 4 days on days 1-4, methylprednisolone (mPSL) (250 mg/d) for 5 days on days 1-5, Ara C (2,000 mg/m²) on day 5, and cisplatin (CDDP) (25 mg/m²/d) for 4 days on days 1-4 (23).

Recent findings showed that CC chemokine receptor 4 (CCR4) is expressed on normal T helper type 27 and regulatory T (Treg) cells and by certain types of T-cell neoplasms. Moreover, CCR4 antibody therapy is currently available for use in refractory ATL patients in Japan (24). Based on the findings of a phase II study that showed a 50% response rate with acceptable toxicity profiles, we administered CCR4 antibody (mogamulizumab) therapy in 8 courses, weekly, at a dose of 1.0 mg/kg (24). The treatment response was judged according to the Japan Clinical Oncology Group (JCOG) treatment response criteria for ATL (6).

This retrospective study was conducted in compliance with good clinical practices and the ethical principles of the Declaration of Helsinki. Prior approval was obtained from the ethics review board at our institution.

Statistical analysis

The Kaplan-Meier method was used to estimate probabilities of OS, and log-rank tests were used to compare OS between ATL subtypes and treatments.
(A) Age distribution of ATL patients

(B) Age distribution according to treatment strategy

Figure 1. Age distribution of ATL patients. Of the 81 patients, 51 (63%) were older than 65 years of age. Age distribution according to each treatment strategy revealed a tendency of advanced age in the following treatment groups (in decreasing order): palliative therapy, CHOP therapy, and intensified chemotherapy consisting of CAP-AMP-VECP therapy or CHOP-VMMV therapy.

Table 2. Clinical Characteristics of ATL Patients Treated with Palliative Therapy.

| Cases | Acute type | Lymphoma type | Age: median [range] | Number of Distribution: numbers | PS | Hypercalcemia | Infiltration of organs | Survival: median (range) |
|-------|------------|---------------|---------------------|---------------------------------|----|---------------|------------------------|--------------------------|
| 25 cases | 14 cases | 11 cases | 55-64:2 | 65-74:6 | 75-84:12 | 85-94:5 | PS:0-2:0% | PS3:8.0% (2/25) | 32% (8/25) | PS4:92.0% (23/25) | Lung:32% (8/25) | Liver:40% (10/25) | Kidney:24% (6/25) | CNS:12% (3/25) | Intestine:4% (1/25) |
|       |            | [56 – 93]    |                     |                                 |    |              |                        |                          |

Results

Baseline patient characteristics

According to the Shimoyama diagnostic criteria, the 99 ATL patients were classified as having acute (47 cases), lymphoma (32 cases), chronic (11 cases), or smoldering type (9 cases) ATL. In the present study, we retrospectively analyzed 81 patients with aggressive type ATL consisting of acute (47 cases), lymphoma (32 cases), and chronic type (2 cases) ATL who required treatment.

The baseline characteristics of all patients are summarized in Table 1. The patient population included 35 men and 46 women, with an age range of 34-93 years (median age, 67.5 years). Patients older than 65 years of age accounted for 63.0% (51/81) of all ATL patients (Fig. 1A).

Clinical characteristics of ATL patients according to initial treatment

According to the treatment decisions described in the patients and methods section, initial treatment, in the absence of disease progression, consisted of CHOP therapy, intensified chemotherapy (VCAP-AMP-VECP therapy or CHOP-VMMV therapy), or palliative therapy.

While most clinical trials exclude palliative care patients, we included such patients in the present study. While focusing on the age, PS, and organ infiltration of ATL, we analyzed the clinical characteristics of 25 ATL patients with palliative therapy. The median age of these patients was 77
years (range, 56-93 years). Age distribution according to the therapy administered revealed a tendency of advanced age with the following treatments in descending order: palliative therapy, CHOP therapy, and intensified chemotherapy (VCAP-AMP-VECP therapy or CHOP-VMMV therapy) (Fig. 1B). Of all the ATL patients treated with palliative therapy, 17 (68%) were over 75 years, 23 (92%) had a PS of 4, and 8 (32%) developed hypercalcemia (32%). In addition, infiltration of the lung (32%), liver (40%), kidney (24%), central nervous system (CNS) (12%), and intestine (10%) was noted (Table 2). Acute and life-threatening dysfunction by organ infiltration led to acute respiratory failure, acute liver dysfunction, acute mental disturbance, uncontrolled hemorrhaging in the intestine, and acute renal failure. Based on the combination of advanced age (>75 years), poor PS (3, 4), and acute life-threatening organ infiltration by ATL, the selection of palliative therapy was finally determined. Consequently, palliative patients had a poor median survival duration of 16 days (range, 1-156 days) (Table 2, Fig. 2B).

The initial systemic chemotherapeutic regimens consisted of CHOP therapy (25 cases), VCAP-AMP-VECP therapy (11 cases), and CHOP/VMMV therapy (20 cases). CHOP therapy was performed for a median of 2 courses (range, 1-6). Intensified chemotherapy consisting of VCAP-AMP-VECP therapy or CHOP-VMMV therapy was also performed for a median of 2 courses (range, 1-4) because of prolonged and progressive cytopenia.

Treatment outcomes of initial treatment

According to Shimoyama’s diagnostic criteria, 50% survival was observed at approximately 6 and 8 months in patients with acute and lymphoma ATL, respectively (Fig. 2A). The median OS of palliative therapy and all chemotherapies was 16 and 277 days, respectively (Fig. 2B). The median survival duration of patients who underwent CHOP or intensified chemotherapy consisting of VCAP-AMP-VECP therapy or CHOP-VMMV therapy was 173 days and 326 days, respectively (Table 4A).
**Figure 3.** A flow cytometric analysis in long-term survivors harboring HLA 2,402 shows the presence of tax-specific CTL cells at densities of 0.1% in case 2 (1,715 days after diagnosis) and 0.6% case 3 (1,780 days after diagnosis), respectively.

**Table 3.** (A) Clinical Characteristics of ATL Patients Treated with Subsequent HSCT Treatment. (B) Clinical Characteristics of ATL Patients Treated with Subsequent Salvage Treatment. (C) Clinical Characteristics of ATL Patients Treated with Subsequent Mogamulizumab Treatment.

### (A) Clinical characteristics of ATL patients treated with subsequent HSCT treatment

| Case | Age | Sex | Subtype | Chemotherapy | Disease status | HSCT (Conditioning) | Source of stem cells | Survival (Days after HSCT) |
|------|-----|-----|---------|--------------|----------------|---------------------|----------------------|-------------------------|
| 1    | 49  | F   | Lymphoma| CHOP-VMMV    | CR             | MAC (TBI/CY)       | CB                   | 138 days (ATL relapse) |
| 2    | 42  | M   | Lymphoma| CHOP-VMMV    | CR             | MAC (TBI/CY)       | CB                   | 135 days (ATL relapse) |
| 3    | 61  | F   | acute   | VCAP-VMP-VECP therapy | PR    | RIC (BU/FLU/TBI) | CB                   | 28 days (ATL relapse) |
| 4    | 44  | F   | acute   | VCAP-VMP-VECP therapy | CR    | MAC (TBI/CY)       | Unrelated HLA full matched BM | 131 days alive |
| 5    | 56  | F   | acute   | VCAP-VMP-VECP therapy | CR    | MAC (TBI/CY)       | Unrelated HLA full matched BM | 203 days alive |
| 6    | 41  | F   | acute   | VCAP-VMP-VECP therapy | CR    | MAC (TBI/CY)       | Unrelated HLA full matched BM | 122 days dead (ATL relapse) |

### (B) Clinical characteristics of ATL patients treated with subsequent salvage treatment

| CHASE, DeVIC, ESHAP | patients | Response after initial treatment | Response after salvage therapy |
|---------------------|----------|----------------------------------|-------------------------------|
| 29                  | PD       | SD:10cases, PD:38cases (Total 48course) |

### (C) Clinical characteristics of ATL patients treated with subsequent mogamulizumab treatment

| Mogamulizumab | Age | Sex | Subtype | Chemotherapy | Response after initial treatment | Response after mogamulizumab | Survival (Days after initiation of mogamulizumab) |
|---------------|-----|-----|---------|--------------|---------------------------------|-----------------------------|----------------------------------|
| Case 1        | 48  | F   | acute   | VCAP-VMP-VECP therapy | PD    | 5course→CR ▶ 7course→PD       | 192 days (ATL relapse in peripheral blood) |
| Case 2        | 71  | F   | acute   | CHOP         | PD    | 5course→CR ▶ relapse          | 83 days (ATL relapse in peripheral blood) |
| Case 3        | 74  | F   | acute   | CHOP         | PD    | 6course→CR                    | 82 days alive |

Abbreviations: HSCT: Hematopoietic stem cell transplantation, CR: complete response, PR: partial response, MAC: myeloablative conditioning, RIC: Reduced-Intensity Conditioning, TBI: total body irradiation, CY: cyclophosphamide, FLU: Fludarabine, BU: busulfan, CB: cord blood, BM: bone marrow
Clinical characteristics of ATL patients who underwent subsequent treatment

As described in the patients and methods section, we performed subsequent treatment involving HSCT for ATL patients who met the criteria of receiving HSCT and performed salvage therapy or mogamulizumab therapy for cases of ATL relapse (Table 3).

Clinical characteristics of ATL patients who underwent HSCT

At diagnosis, among the 56 patients who underwent chemotherapy, 19 met the indication criteria (age <60 years) for HSCT. Of these, 15 patients were treated with intensified chemotherapy consisting of VCAP-AMP-VECP therapy or CHOP-VMMV therapy, 3 patients were treated with CHOP therapy, and 1 patient was treated with palliative therapy. Consequently, 15 of the 19 ATL patients attained a response (CR or PR). The reasons for contraindication of HSCT were poor PS status of 4 (2 cases), uncontrollable schizophrenia (2 cases), and patient’s decision (2 cases). Thus, 6 of the 19 ATL patients underwent HSCT. The clinical characteristics of the 6 ATL patients with HSCT are shown in Table 3A. The source of the stem cells for transplantation was CB in 3 cases and UR-BM in 3 cases. Among the 6 HSCT patients, 2 patients who received stem cells from UR-BM attained CR without relapse; however, the remaining 4 patients, including 3 HSCT patients who received stem cells from CB, eventually relapsed. These patients did not respond to immediate cessation of immunosuppressants, and subsequent donor lymphocyte infusion (DLI) or salvage therapy was not performed because of the aggressive progression of ATL and poor PS. Consequently, our retrospective study showed that only 7.4% (6/81) of all ATL patients received allogeneic HSCT and only 2 out of 6 patients attained CR without relapse.

Clinical characteristics of ATL patients who received conventional salvage therapy

Although the initial systemic chemotherapy consisting of CHOP therapy or intensified chemotherapy resulted in high response rate (Table 3B), the initial systemic chemotherapy was associated with serious problems, such as short duration of remission and subsequent relapse. Before approval was granted for mogamulizumab therapy in relapsed ATL patients, we performed salvage therapy consisting of CHASE, DeVIC, ESHAP, or CHOP therapy (Table 3B). Salavage therapy was performed in 29 ATL patients for a median of 2 courses (range, 1-7). Salvage therapies showed poor outcomes, and none of the 29 refractory ATL patients showed any positive response [stable disease (SD), CR, or PR].
Clinical characteristics of ATL patients who received mogamulizumab therapy

After approval of mogamulizumab was granted on March 2012 in Japan, 3 CCR4-positive ATL patients with PD following initial chemotherapy underwent 8 courses of mogamulizumab therapy (Table 3C). Mogamulizumab therapy led to a response in all 3 patients (PR, 1 case; CR, 2 cases) (Table 3C). In 2 acute type ATL cases, mogamulizumab therapy markedly diminished the number of ATL cells in the peripheral blood after 2 treatment courses. However, the duration of progression-free survival was short, with two cases relapsing 21 days after CR or 22 days after PR during treatment. However, in the remaining 1 case, mogamulizumab therapy led to a CR with 82 days survival after relapse.

Clinical characteristics of long-term survivors with chemotherapy only

The data on the few long-term survivors (>5 years) of this study revealed the clinical features, laboratory findings, and histological findings associated with long-term survival. Our long-term survivors showed a tendency to be female, have lymphoma type ATL, and were low and intermediate risk based on the ATL prognostic index (ATL-PI) (25) despite the presence of CSIII disease (Table 4B). In order to elucidate the relationship between long-term survival and the presence of tax-specific cytotoxic T lymphocyte (CTL) cells, we analyzed the presence of CTL cells after systemic chemotherapy by flow cytometry in two ATL patients harboring HLA 2402. The presence of tax-specific CTL cells was detected at a concentration of 0.1% in case 2 at 1,715 days after diagnosis and 0.6% in case 3 at 1,780 days after diagnosis (Fig. 3). However, we did not analyze the presence of CTL cells before chemotherapy in these ATL patients. Moreover, we also did not study the presence of CTL cells among the non-surviving ATL patients.

Immune-compromised infections

Representative immune-compromised infection complications were detected in 5 ATL patients: Pneumocystis ji-rovecii pneumonia in 1 case, cryptococcal meningitis in 1 case, and CMV pneumonia in 3 cases. We focused our analysis on the 2 cases that achieved remission after CMV infection. In 2 cases with a complication of severe CMV pneumonia, self-remission (CR and PR) of acute type ATL was achieved. In 1 case harboring HLA 2402, tax-specific CTL cells were detected at a concentration of 0.1%. However, both cases presented with prolonged CMV antigenemia requiring ganciclovir treatment. Consequently, subsequent HSCT was not performed on the 2 cases.

Discussion

To resolve the discrepancy of remarkable advances in ATL treatment (1-16) and the unchanged annual deaths associated with ATL (17), it may be essential to clarify the current clinical features and treatment outcomes of ATL in the real world.

In this retrospective study, we described the current clinical characteristics and treatment outcomes of ATL in the real world at Miyazaki prefecture, which included: (1) an increase in the median age at onset of ATL compared to earlier studies; (2) a persistently high proportion of patients undergoing palliative therapy due to complications of advanced age, poor PS, hypercalcemia, and infiltration of systemic organs by ATL; (3) a small number of long-term survivors (>5 years) treated only with chemotherapy whose characteristics indicated a predominance towards low and intermediate risk according to the ATL-PI, female sex, and lymphoma type ATL; (4) a small proportion of patients undergoing HSCT; and (5) a persistently poor prognosis due to (1)-(4). Consequently, in our institution, ATL patients exhibited heterogeneous clinical features that were treated with heterogeneous treatment strategy including palliative therapy, chemotherapy, and HSCT.

We thus focused and discussed three issues associated with the current clinical treatment strategy of palliative therapy, chemotherapy, and HSCT in contrast to previous reports (6, 7, 12-16, 24).

The first issue is related to the palliative therapy group; a high proportion of patients were treated by palliative therapy in this study. Although most clinical trials excluded palliative care patients, our study showed that ATL patients who received palliation had a tendency to present with advanced age, poor PS and systemic infiltration of organs. Based on the combination of advanced age (>75 years), poor PS (3, 4), and acute life-threatening organ infiltration by ATL, the selection of palliative therapy was finally determined. However, this therapy group had poor outcomes. Therefore, another approach may be essential before the onset of ATL for elderly ATL patients. Recently, a phase III study using a combination of interferon-alpha (IFN) and zidovudine (AZT) was initiated in September 2013 in Japan for the early intervention of symptomatic smoldering type ATL and chronic type ATL (JCOG1111, IFN/AZT vs. WW for indolent ATL P-III). The intervention of indolent-type ATL cases provides promise for the prevention of progression to aggressive ATL in elderly patients.

The second issue is related to the chemotherapy treatment group. Consistent with previous reports (6, 7), the chemotherapy group in our study showed an equivalent response rate and OS of ATL. However, in a majority of the patients treated with chemotherapy, the short duration of remission, early relapse after remission, and refractory to salvage therapy led to no plateau phase and poor outcome. However, in our study, a small proportion of long-term survivors (>5 years) were found to have a predominance of low and intermediate risk of ATL-PI, to be female, and to have lymphoma type ATL. Several reports showed that tax-specific CTL cells may be promising targets for molecular therapy, with long-term persistence, in ATL patients who have re-
ceived HSCT (26, 27). Our data further suggests that even among patients receiving chemotherapy, the presence of CTL cells may partially contribute to long-term survival, consistent with previous reports (26, 27). In addition, mogamulizumab therapy led to transient response for refractory ATL in our patients. Recently, a phase II study of mogamulizumab plus VCAP-AMP-VECP therapy revealed a response rate of 86% and progression-free survival (PFS) of 259 days (28). Therefore, mogamulizumab-combined chemotherapy may be a promising treatment option for ATL patients.

The third issue is related to the HSCT treatment group. Among ATL patients annually diagnosed (1,100 patients in 2011 in Japan), only 5-10% (135 patients in 130 facilities, Japan) received allogeneic HSCT, with 3-5% achieving long-term survival (29). Consistent with a previous report (29), in our study, only a small proportion of patients underwent HSCT. The reasons for contra-indication of HSCT included disease control, poor PS, CMV infection, uncontrollable schizophrenia, or patient’s decision. Therefore, achieving an increase in response, maintaining PS during treatment, and monitoring CMV antigenemia are essential to increase the number of patients who receive HSCT. Moreover, several clinical studies and reports recently revealed promising data on the feasibility of reduced-intensity hematopoietic stem cell transplantation (RIST) in elderly ATL patients (13, 14). Increasing the number of RIST for elderly ATL patients may thus be essential to increase the likelihood of HSCT and to improve poor outcomes. In the HSCT group, relapsing after HSCT therapy was the main problem. In the present study, three out of four non-surviving patients receiving HSCT using stem cells from CB finally relapsed despite the presence of a CR status before the HSCT. In previous reports, multivariate analyses revealed that poor OS is related to risk factors such as advanced age (>50 years), poor PS, male sex, status other than CR, use of CB, and unrelated donors (15, 16). Patients who receive HSCT with these prognostic factors may need to be carefully followed. With regard to treatment for relapsed ATL patients after HSCT, our 4 cases did not receive further treatment, except for the immediate cessation of immunosuppressants because of the aggressive progression of ATL and poor PS. However, successful mogamulizumab treatment for relapsed ATL after HSCT has been recently reported, thus suggesting that mogamulizumab treatment may be a promising subsequent therapeutic option for relapse in ATL patients after HSCT (30). In the future, it may be crucial to determine which type of conditioning (MAC or RIST), source of stem cells (BM, peripheral blood, or CB), and therapeutic strategy for the relapse after HSCT in HSCT patients is suitable for ATL treatment.

In conclusion, our study showed that the OS of ATL remains poor due to a high proportion of patients treated by palliative therapy, a small proportion of long-term survivors (>5 years) with chemotherapy only, and a small proportion of patients receiving HSCT. In the future, early diagnosis and prompt intervention by chemotherapeutic treatments, such as mogamulizumab-combined chemotherapy and subsequent RIST for elderly ATL patients, may be crucial to prevent the exacerbation of ATL and improve the outcome of ATL. This retrospective study illustrates the current clinical features, treatment strategies, and treatment outcomes for ATL in clinical practice.

The authors state that they have no Conflict of Interest (COI).

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