Recent advances in the treatment of adult T-cell leukemia-lymphomas

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Adult T-cell leukemia-lymphoma (ATL) is a mature T-cell neoplasm caused by human T-cell leukemia virus type-I (HTLV-1). Following the initial report by Uchiyama et al., many key discoveries concerning the mechanism of leukemogenesis of ATL have been made in association with the HTLV-1 tax and HTLV-1 basic leucine zipper factor genes. Several clinical manifestations of ATL are known and may be classified into four clinical subtypes based on the presence of organ involvement and the results of blood work-up. This classification is currently used as the basis for therapeutic strategies.

Therapeutic interventions, including intensive chemotherapy for aggressive ATL, are not associated with satisfactory outcomes, mainly because ATL cells are often resistant to chemotherapeutic agents; moreover, patients with ATL frequently suffer from a number of opportunistic infections. We reported for the first time that allogeneic hematopoietic stem cell transplantation (allo-HSCT) improved overall survival (OS) in ATL patients.

In Europe and USA, antiviral therapy has been frequently applied for ATL patients since the therapeutic efficacy of zidovudine (AZT) and interferon-α (IFN) has been demonstrated. More recently, the mechanism of action of AZT combined with IFN (AZT/IFN) has been partially elucidated. Antiviral therapy has received greater attention in Europe and USA than in Japan. Finally, new molecular targeted agents are under investigation in patients with ATL.

Herein, we review current treatments for ATL, along with previous and future therapies.

Epidemiology

Approximately 10–20 million people are infected with HTLV-1 worldwide; endemic areas include Central Africa, South America, the Caribbean basin, Iran, south-western Japan and Melanesia. In Japan, approximately 1.1 million individuals are infected with HTLV-1 and approximately 1000 HTLV-1 carriers develop ATL each year.

In late 2000, a decrease in the prevalence of HTLV-1 carriers has been observed in the Kyushu district (south-western island of Japan, an endemic area for ATL); however, the prevalence is increasing in several regions in the non-endemic areas. The age-standardized incidence rates of ATL in the Honshu region of Japan and the USA, both of which are considered non-endemic areas, are increasing significantly, although no changes in incidence have been observed in the Kyushu district. These results suggest that HTLV-1 is spreading through the migration of carriers from endemic to non-endemic areas. The mortality (per 100 000 person-years)
of patients with ATL decreased from 1.86 (95% confidence interval [CI]: 1.84–1.87) to 1.41 (95% CI: 1.40–1.43) in Kyushu during the period of 2000–2009, and from 0.22 (95% CI: 0.22–0.23) to 0.14 (95% CI: 0.16–0.17) in other areas of Japan from 2003–2009, and these trends are statistically significant.\(^{(13)}\) The number of allo-HSCT performed in Japan has increased since 2000.\(^{(13)}\) A significant inverse correlation was observed between the decreasing mortality trend and the increasing number of allo-HSCT procedures. The decreasing trend in mortality observed in ATL patients might be associated with allo-HSCT.\(^{(13)}\)

**Diagnosis and Clinical Subtype**

A diagnosis of ATL is made by anti-HTLV-1 positivity in sera and by confirming the presence of a mature T-cell malignancy. The identification of monoclonal integration of HTLV-1 proviral DNA in tumor cells by Southern blot analysis is required to confirm a diagnosis of ATL.

Adult T-cell leukemia-lymphoma is divided into four clinical subtypes (acute, lymphoma, chronic and smoldering) according to leukemic manifestation in the blood, organ involvement, serum lactate dehydrogenase (LDH) levels and corrected serum calcium levels (Table 1).\(^{(5)}\) Chronic type is divided into two subtypes: the unfavorable chronic type with at least one poor prognostic factor and the favorable chronic type with no poor prognostic factors. Poor prognostic factors include three factors: serum LDH, serum albumin, and corrected serum calcium levels (Table 1).\(^{(5)}\)

**Prognostic Factors and Stratification**

The Lymphoma Study Group has identified five prognostic factors: age, total number of involved lesions, serum calcium level, serum LDH level and performance status (PS).\(^{(16)}\) When ATL is stratified into three different groups (i.e. low risk group and high risk group based on the combination of prognostic factors, and extremely high risk group with high levels of serum calcium), OS is clearly different between the three groups. Nonetheless, these stratifications are not practical clinically as the classification system is rather complicated. In order to provide a more clinically useful system, Shimoyama devised a new clinical classification scheme for the four subtypes mentioned above.\(^{(5)}\)

Several research groups in Japan have reported other factors that may also influence OS in ATL patients. These include deletion of p16, lung resistance-related protein and multi-drug resistance associated protein genes, eosinophilia, and expression of CC chemokine receptor 4 (CCR4) and serum interleukin (IL)-5.\(^{(17)}\)

Recently, the Ann Arbor clinical stage, PS, and three continuous variables, age, serum albumin and soluble interleukin-2 receptor, were identified as independent prognostic factors in a multicenter retrospective analysis of 807 patients with newly diagnosed, acute-type and lymphoma-type ATL. Based on these results, Katsuya et al.\(^{(18)}\) propose a prognostic index for acute-type and lymphoma-type ATL.

**Treatment of Adult T-cell Leukemia-lymphoma**

The current treatment strategy for patients with ATL is shown in Figure 1. Treatment is based on the clinical subtype. Patients with aggressive ATL, such as acute, lymphoma or chronic types, with at least one poor prognostic factor should receive early chemotherapy. In the USA and Europe, antiviral therapy using AZT/IFN is the standard treatment for leuemic-type ATL. In Europe, chemotherapy is the first-line therapy for lymphoma-type ATL, because OS with antiviral therapy alone is very short.\(^{(19)}\)

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**Table 1. Diagnostic criteria for clinical subtype of adult T-cell leukemia-lymphoma**

|                     | Smoldering | Chronic‡ | Lymphoma | Acute |
|---------------------|------------|-----------|-----------|-------|
| Anti-HTLV-1 antibody| +          | +         | +         | +     |
| Lymphocyte (× 10⁹/L)| <4         | ≥4        | <4        | †     |
| Abnormal T-lymphocytes| ≥5%       | +††       | ≤1%       | +††   |
| Flower cells of T-cell marker | Occasionally | Occasionally | No     | +    |
| LDH                 | ≤1-5N      | ≤2N       | †         | †     |
| Corrected Ca (mmol/L) | <2-74   | <2-74     | †         | †     |
| Histology-proven lymphadenopathy | No    | †         | +        | †     |
| Tumor lesion        |            |           |           |       |
| Skin                | †          | †         | †         | †     |
| Lung                | †          | †         | †         | †     |
| Lymph node          | No         | †         | Yes       | †     |
| Liver               | No         | †         | †         | †     |
| Spleen              | No         | †         | †         | †     |
| CNS                 | No         | No        | †         | †     |
| Bone                | No         | No        | †         | †     |
| Ascites             | No         | No        | †         | †     |
| Pleural effusion    | No         | No        | †         | †     |
| GI tract            | No         | No        | †         | †     |

†No essential qualification except terms required for other subtype(s). ††No essential qualification if other terms are fulfilled, but histology-proven malignant lesion(s) is required in case abnormal T-lymphocytes are less than 5% in peripheral blood. ‡Chronic type is divided into two subtypes: the unfavorable chronic type with at least one poor prognostic factor and the favorable chronic type with no poor prognostic factors. Poor prognostic factors include three factors: serum LDH level, serum albumin, and corrected serum calcium levels. §In case abnormal T-lymphocytes are less than 5% in peripheral blood, histology-proven tumor lesion is required. Ca, calcium; CNS, central nervous system; GI, gastrointestinal; HTLV-1, human T-cell leukemia virus type-I; LDH, lactate dehydrogenase; N, normal upper limit. Source: Shimoyama (1991).
Chemotherapy

Several chemotherapy combinations have been investigated for ATL patients in Japan, although the median OS range was only 6–8.5 months. The Japan Clinical Oncology Group-Lymphoma Study Group (JCOG-LSG) has conducted a number of clinical trials for ATL patients in Japan, with complete response (CR) rates of 17–43% and median OS of 5–13 months in prospective multicenter studies. The JCOG-LSG conducted a randomized clinical trial in patients with aggressive ATL in which a VCAP-AMP-VECP regimen (Fig. 2) was compared to a biweekly doxorubicin, cyclophosphamide, vincristine, and prednisone (CHOP14) regimen. The VCAP-AMP-VECP regimen reduced one course of VCAP-AMP-VECP from the original LSG15 regimen and added etoposide to the intrathecal administration of methotrexate and prednisone as a prophylaxis against central nervous system (CNS) relapse. The CR rate and median OS of the VCAP-AMP-VECP regimen and CHOP14 regimen were 40% (95% CI: 27.6–54.2) versus 25% (95% CI: 14.5–37.3), and 13 versus 11 months, respectively. The CR rate of the VCAP-AMP-VECP regimen was significantly higher than that of CHOP14. In terms of the OS, there was no significant difference in the two groups (hazard ratio [HR] = 0.751, 95% CI: 0.50–1.13). The VCAP-AMP-VECP regimen is considered a standard chemotherapeutic regimen for aggressive ATL in Japan.

Stem Cell Transplantation

In general, autologous HSCT has not been successful because of ATL relapses or infectious complications. We and other Japanese researchers have reported that allo-HSCT could improve the outcome of ATL, mainly using conventional myeloablative regimens (MAC); however, high transplant-related mortality poses a challenge.

Therefore, allo-HSCT with reduced intensity conditioning regimens (RIC) was prospectively evaluated. Okamura et al. report the safety and feasibility of allo-HSCT with RIC using peripheral blood stem cells from an HLA-matched sibling donor in older patients with ATL who achieved remission after chemotherapy. A total of 29 patients were registered, and the 5-year OS rate was 34% (95% CI: 18–51), indicating the potential curability of the disease. Unrelated bone marrow (uBM) and cord blood transplantation with RIC were also prospectively evaluated as alternative strategies to allo-HSCT; follow up is currently under way.

By 2012, more than 1000 ATL patients had received various types of allo-HSCT. Currently, approximately 120 ATL patients undergo allo-HSCT each year in Japan. Based on the incidence rate, approximately 10% of ATL patients receive allo-HSCT each year. Several related aspects have been reported in a nationwide retrospective study. Based on the stem cell sources, the 3-year OS rate was highest for patients with related HLA-matched donors (41%, 95% CI: 33–49), followed...
by those with uBM (39%, 95% CI: 29–49).\(^{(28)}\) In terms of the effect of acute graft-versus-host-disease (GVHD) on OS, grade I/II acute GVHD was significantly associated with a longer OS.\(^{(29)}\) Regarding the effect of the conditioning regimen intensity on OS, although no significant difference was observed in the OS between MAC and RIC, a trend for superior OS was observed with RIC in older patients.\(^{(30)}\) Bazarbachi et al.\(^{(31)}\) report the results from the European Group for Blood and Marrow Transplantation’s Lymphoma Working Party, and allo-HSCT might salvage ATL patients in non-Japanese patients.

**Immunotherapy**

Antitumor immune system activity has also been recognized in ATL patients who have received allo-HSCT.\(^{(20)}\) Cytotoxic T-cells that targeted the HTLV-1 specific tax protein were detected in patients who were in remission after allo-HSCT.\(^{(32)}\)

The discontinuation of immunosuppressive agents or donor lymphocyte infusions was effective in some ATL patients who relapsed after allo-HSCT; many of them developed GVHD subsequently.\(^{(33,34)}\) The graft versus (Gv)-ATL effect, in particular the graft versus-taxon Gv-taxon effect after allo-HSCT, has been reported in ATL patients.\(^{(32)}\) Therefore, immunotherapy targeting the tax protein may be effective in patients whose tumor cells express the tax protein. Indeed, a vaccine targeting the HTLV-1 specific tax protein was reported previously.\(^{(5)}\) Bazarbachi et al.\(^{(31)}\) report the results from the European Group for Blood and Marrow Transplantation’s Lymphoma Working Party, and allo-HSCT might salvage ATL patients in non-Japanese patients.

**Molecular Targeted Therapy**

Anti-CCR4 antibody therapy. The overexpression of CCR4 has been reported in tumor cells of various lymphoid neoplasms. The ratio of expression varies among different disease entities and is higher in mature T-cell and NK-cell neoplasms. Approximately 90% of ATL cases are CCR4-positive.\(^{(40)}\) CCR4 expression has also been shown to affect the prognosis of ATL patients; multivariate analysis revealed that CCR4 positivity was a significant unfavorable prognostic factor.\(^{(40)}\)

Mogamulizumab (KW-0761) is a first-in-class defucosylated humanized anti-CCR4 monoclonal antibody that has been generated by protein engineering;\(^{(41)}\) mogamulizumab shows highly potent ADCC activity because of its high affinity of binding to effector cells, including NK cells. Based on the phase I study, a phase II study for CCR4-positive relapsed ATL was conducted in Japan wherein 1.0 mg/kg of mogamulizumab was intravenously administered once a

| Protocol A (VCAP) | Dose | Day | 8 | 15 | 16 | 17 |
|------------------|------|-----|---|----|----|----|
| VCR (vincristine)| 1 mg/m² | 1 |   |    |    |    |
| CPA (cylophosphamide)| 350 mg/m² | 1 |  |  |  |  |
| ADM (doxorubicin) | 40 mg/m² | 1 |  |  |  |  |
| PSL (prednisone) | 40 mg/m² | 1 |  |  |  |  |

| Protocol B (AMP) |  |  |  |  |  |  |
|------------------|-----------------|---|---|---|---|---|
| ADM (doxorubicin) | 30 mg/m² | I |  |  |  |  |
| MCNU (ranimustine) | 60 mg/m² | I |  |  |  |  |
| PSL (prednisone) | 40 mg/m² | I |  |  |  |  |

| Protocol C (VECP) |  |  |  |  |  |  |
|------------------|-----------------|---|---|---|---|---|
| VDS (vindeistine) | 2.4 mg/m² | I |  |  |  |  |
| ETO (etoposide) | 100 mg/m² | I | I | I | G-CSF |
| CBDOCA (carboplatin) | 250 mg/m² | I |  |  |  |  |
| PSL (prednisone) | 40 mg/m² | I | I | I | I |
| Reference | Patient Number | Median age (range) | Sex M/F | Subtype | Donor HTLV-1 Ab | Stem cell source | Disease Status at SCT | Conditioning regimen | Cause of death | Outcome |
|-----------|----------------|-------------------|---------|---------|----------------|----------------|----------------------|----------------------|---------------|---------|
| Utsunomiya (BMT, 2001) | 10 | 45 (33–51) | 7/3 | Acute: 8 Lymphoma: 1 Other: 1 | MSD: 9 Neg: 7 | BM: 8 PR: 5 | CR: 4 MAC: 10 TRM: 4 | Median leukemia-free survival 17.5± M (range 3.7–34.4±) |
| Kami (BJH, 2003) | 11 | 47 (15–59) | 7/4 | Acute: 5 Lymphoma: 4 Other: 2 | MSD: 9 Neg: 9 | BM: 7 PR: 1 | CR: 6 MAC: 9 TRM: 7 | 1Y-OS 54.5 ± 30.0% |
| Fukushima (Leukemia, 2005) | 40 | 44 (28–53) | 22/18 | Acute: 30 Lymphoma: 10 | MSD: 27 Neg: 27 | BM: 21 PR: 4 | CR: 15 MAC: most cases TRM: 16 | 3Y-OS 45.3% |
| Kato (BBMT, 2007) | 33 | 49 (24–59) | 18/15 | Acute: 20 Lymphoma: 7 NE: 6 | MUD: 33 Neg: 33 | BM: 33 CR + PR: 15 MAC: 27 TRM: 9 | 1Y-OS 49.5% |
| Shiratori (BBMT, 2008) | 15 | 57 (41–66) | 3/12 | Acute: 6 Lymphoma: 8 Other: 1 | MSD: 10 Neg: 13 | BM: 8 PR: 5 | CR: 9 MAC: 5 TRM: 2 | 3Y-OS 73.3% |
| Nakase (BMT, 2006) | 8 | 49 (45–59) | 2/6 | Acute: 5 Lymphoma: 3 PMUD: 5 | MUD: 3 Neg: 8 | BM: 8 CR: 6 MAC: 5 | TRM: 2 Median OS 20M (range 0-43) |
| Nakamura (IJH, 2012) | 10 | 51 (31–64) | 6/4 | Acute: 9 Lymphoma: 1 | PMUD: 10 Neg: 10 | UCB PR: 4 SD: 3 | CR: 2 MAC: 6 RIC: 4 | 2Y-OS: 40% (95% CI 67-12) |
| Fukushima (IJH, 2013) | 27 | 52 (41–63) | 18/9 | Acute: 17 Lymphoma: 10 PMUD: 26 | MUD: 1 Neg: 27 | UCB CR: 5 PR: 11 RIF: 5 REL: 6 | MAC: 9 RIC: 18 TRM: 10 | 3Y-OS: 27.4% |
| Bazarbachi (BMT, 2014) | 17 | 47 (21–58) | 9/8 | Acute: 5 Lymphoma: 10 Chro/Smold: 2 | MUD: 6 Neg: 6 | ND ND CR: 9 MAC: 4 | TRM: 8 ATL: 8 | 3Y-OS: 34.3% |

ATL, adult T-cell leukemia-lymphoma. BBMT, Biology of Blood and Marrow Transplantation; BJH, British Journal of Haematology; BMT, bone marrow transplantation; Chro/Smold, chronic/smoldering; CR, complete remission; GVHD, graft-versus-host disease; IJH, International Journal of Hematology; M, month; MAC, myeloablative conditioning; MSD, HLA-matched sibling donor; MUD, HLA-matched unrelated donor; NC, no change; ND, not described; NE, not evaluable; Neg, negative; NR, no response; OS, overall survival; PD, progressive disease; Posi, positive; PMRD, HLA partially matched related donor; PMUD, HLA partially matched unrelated donor; PR, partial remission; RIC, reduced intensity conditioning; SCT, stem cell transplantation; SD, stable disease; TRM, transplant-related mortality; UCB, unrelated cord blood; UnK, unknown.
week for 8 weeks; of the 26 patients evaluable for efficacy assessment, the ORR was 50% (95% CI: 30–70), and response rates according to disease lesions were 100% for blood, 63% for skin, and 25% for nodal and extranodal lesions. The median progression-free survival and OS were 5.2 and 13.7 months, respectively. Subsequently, a randomized clinical trial was conducted for evaluating VCAP-AMP-VECP treatment with or without mogamulizumab in newly diagnosed CCR4-positive aggressive ATL patients in Japan. Combination therapy with VCAP-AMP-VECP plus mogamulizumab demonstrated a CR rate of 52% (95% CI: 33–71), which was 19% higher than treatment with VCAP-AMP-VECP alone (33%, 95% CI: 16–55). Although mogamulizumab was very effective for relapsed ATL, adverse drug reactions, including infusion reaction (89%) and skin rash (63%), were frequently observed in the phase II study. Severe skin rash was observed occasionally, and one patient developed Stevens-Johnson syndrome during the phase II study.

**Molecular targeted therapy with small molecules.** Recently, molecular targeted therapy with small molecules, such as tyrosine kinase inhibitors, angiogenesis inhibitors and proteasome inhibitors, has been applied for various malignancies. The proteasome inhibitor bortezomib has been reported to suppress the growth of ATL cell lines and freshly isolated ATL cells, a trial for relapsed or refractory ATL patients is currently under way in Japan to investigate the clinical efficacy of bortezomib.

**Supportive Therapy**

Hypercalcemia associated with disease progression and opportunistic infections caused by immunodeficiency are problematic events in ATL patients. Patients with hypercalcemia need immediate treatment with hydration, antiuretics, calcitriol, steroids and bisphosphonates. Furthermore, urgent chemotherapy using anti-cancer agents for ATL is needed in severe cases of hypercalcemia. As CNS relapse is known to occur frequently in ATL patients, the intrathecal administration of the anti-cancer agents methotrexate, cytarabine and prednisone is required for prophylaxis. Opportunistic infections from bacteria, fungi, virus, protozoans and parasites are frequently observed in ATL patients, and appropriate treatment is needed. In Japan, prophylactic treatment includes the use of fluconazole for *Candida*, itriconazole for *Aspergillus* and trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii*.

**Recent Findings of Genomic Heterogeneity of Adult T-cell Leukemia-lymphoma Cells**

The initial pathogenic event for ATL is HTLV-1 integration; however, additional genetic alterations in ATL have also been implicated in its pathogenesis. Umino *et al.* recently reported the clonal heterogeneity of ATL tumor cells involving different genomic alterations; they demonstrated that these cells originated from a common cell. It was suggested that approximately 70% of ATL cases undergo clonal evolution, and that genetic instability may attribute to the accumulation of genomic alterations. The existence of multiple clones with genomic instability is one factor that renders ATL cells resistant to conventional chemotherapy. Even if a proportion of cells are killed by chemotherapy, there is always the possibility that a new resistant clone will emerge. Therefore, it is feasible to use allo-HSCT that can cure ATL patients by eliminating the HTLV-1-integrated recipient ATL clones through immune reaction, and by replacing the hematopoietic system with the donor type. Whole genome sequencing revealed that carriers have $10^5$ to $10^7$ orders of distinct clones with different HTLV-1 integration sites, and that most clones harbored one copy of HTLV-1. This indicates that HTLV-1 carriers potentially have $10^3$ to $10^5$ malignant clones. If the number of pre-malignant cells increases, there is a greater possibility that malignant transformation can occur. Therefore, it is important to reduce the number of pre-malignant cells in carriers of HTLV-1 in order to prevent the development of ATL.

**Prevention of Adult T-cell Leukemia-lymphoma Development**

An ongoing nationwide prospective investigation (Joint Study on Predisposing Factors of ATL Development) was initiated in 2001 to identify HTLV-1 carriers with the highest risk of developing ATL. Four risk factors have been associated with ATL development in HTLV-1 carriers, including age ≥40 years, high HTLV-1 proviral loads in peripheral blood mononuclear cells, family history of ATL, and any clinical signs or symptoms. Although it is obviously very important to prevent the development of ATL in HTLV-1 carriers with any of these risk factors, there are currently no available means towards this end. The prevention of HTLV-1 infection is also of utmost importance because ATL is caused by HTLV-1 infection. HTLV-1 infection is thought to be transmitted by breastfeeding from the mother to infant, sexual intercourse or blood transfusion. The incidence of ATL development in HTLV-1 carriers differs according to the route of infection. A nationwide prospective study is currently under way in Japan using three different nursing methods: cessation of breastfeeding, short nursing periods and ordinary nursing.

**Future Directions**

Histone deacetylase (HDAC) inhibitors, such as vorinostat (suberoylanilide hygroxamic acid: SAHA), panobinostat (LBH-589) and MS-275, have been recognized for their abilities to inhibit HTLV-1-infected cell lines and freshly isolated ATL cells. Clinical use of these HDAC inhibitors for the treatment of ATL patients is expected.

Furthermore, various combinations of treatment, including chemotherapy, allo-HSCT, immunotherapy and molecular targeted therapies may help to cure a higher proportion of ATL patients in the future.

**Conclusions**

Although new therapeutic options are gradually improving the curability of ATL, treatment remains challenging for ATL patients. Nevertheless, to increase the ATL cure rate, rigorous investigation is necessary for optimizing therapeutic combinations, prevention of ATL development in HTLV-1 carriers, and reduction in the number of HTLV-1 carriers.

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