(2) M-FEPA (methotrexate, vindesine, cyclophosphamide, prednisone, and doxorubicin), and (3) VEPP-B, (vincristine, etoposide, procarbazine, prednisone, and bleomycin) [104]. The CR rate for ATL patients was improved from 28% (JCOG8101) to 43% (JCOG8701); however, the CR rate was significantly lower in ATL than in B-cell NHL and PTCL ($P<0.01$). Patients with ATL still showed a poor prognosis, with a median survival time of 8 months and a 4-year survival rate of 12%.

The disappointing results with conventional chemotherapies have led to a search for new active agents. Multicenter phase I and II studies of pentostatin (2′-deoxycoformycin, a inhibitor of adenosine deaminase) were conducted against ATL in Japan [108]. The phase II study revealed a response rate of 32% (10 of 31) in cases of relapsed or refractory ATL (two CRs and eight PRs).

These encouraging results prompted the investigators to conduct a phase II trial (JCOG9109) with a pentostatin-containing combination (LSG11) as the initial chemotherapy [105]. Patients with aggressive ATL—that is, of the acute, lymphoma, or unfavorable chronic type—were eligible for this study. Unfavorable chronic-type ATL, defined as having at least one of three unfavorable prognostic factors (low serum albumin level, high LDH level, or high BUN), has an unfavorable prognosis similar to that for acute- and lymphoma-type ATL. A total of 62 untreated patients with aggressive ATL (34 acute, 21 lymphoma, and 7 unfavorable chronic type) were enrolled. A regimen of 1 mg/m^2 vincristine on days 1 and 8, 40 mg/m^2 doxorubicin on day 1, 100 mg/m^2 etoposide on days 1 through 3, 40 mg/m^2 prednisolone (PSL) on days 1 and 2, and 5 mg/m^2 pentostatin on days 8, 15, and 22 was administered every 28 days for ten cycles. Among the 61 patients evaluable for toxicity, four patients (7%) died of infections, two from septicemia, and two from cytomegalovirus pneumonia. Among the 60 eligible patients, there were 17 CRs (28%) and 14 partial responses (PRs) (overall response rate [ORR]=52%). The median survival time was 7.4 months, and the estimated 2-year survival rate was 17%. The prognosis in patients with ATL remained poor, even though they were treated with a pentostatin-containing combination chemotherapy.

In 1994, JCOG initiated a phase II trial (JCOG9303) of an eight-drug regimen (LSG15) consisting of vincristine, cyclophosphamide, doxorubicin, prednisone, ranimustine, vindesine, etoposide, and carboplatin for untreated ATL [106]. Dose intensification was attempted with the prophylactic use of granulocyte colony-stimulating factor (G-CSF). In addition, non-cross-resistant agents such as ranimustine and carboplatin, and intrathecal prophylaxis with MTX and PSL were incorporated. Ninety-six previously untreated patients with aggressive ATL were enrolled: 58 acute, 28 lymphoma, and 10 unfavorable chronic types. Approximately 81% of the 93 eligible patients responded (75/93), with 33 patients obtaining a CR (35%). The overall survival rate of the 93 patients at 2 years was estimated to be 31%, with a median survival time of 13 months. Grade 4 neutropenia and thrombocytopenia were observed in 65% and 53% of the patients, respectively, whereas grade 4 non-hematologic toxicity was observed in only one patient.

To confirm whether the LSG15 regimen is a new standard for the treatment of aggressive ATL, JCOG conducted a phase III trial comparing modified (m)-LSG15 with biweekly CHOP (cyclophosphamide, hydroxy-doxorubicin, vincristine [Oncovin], and prednisone), both supported with G-CSF and intrathecal prophylaxis [107].

mLSG15 in JCOG9801 was a modified version of LSG15 in JCOG9303, consisting of three regimens: VCAP [VCR 1 mg/m^2 (maximum 2 mg), CPA 350 mg/m^2, ADM 40 mg/m^2, PSL 40 mg/m^2] on day 1, AMP [ADM 30 mg/m^2, MCNU 60 mg/m^2, PSL 40 mg/m^2] on day 8, and VECP [VDS 2.4 mg/m^2 on day 15, ETP 100 mg/m^2 on days 15–17, CBDCA 250 mg/m^2 on day15, PSL 40 mg/m^2 on days 15–17] on days 15–17, and the next course was to be started on day 29 (Figure 8.3). The modifications in mLSG15 as compared to LSG15 were as follows; (1) the total number of cycles was reduced from seven to six because of progressive cytopenia, especially thrombocytopenia, after repeating the VCAP-AMP-VECP therapy, (2) cytarabine 40 mg was used with MTX 15 mg and PSL 10 mg for

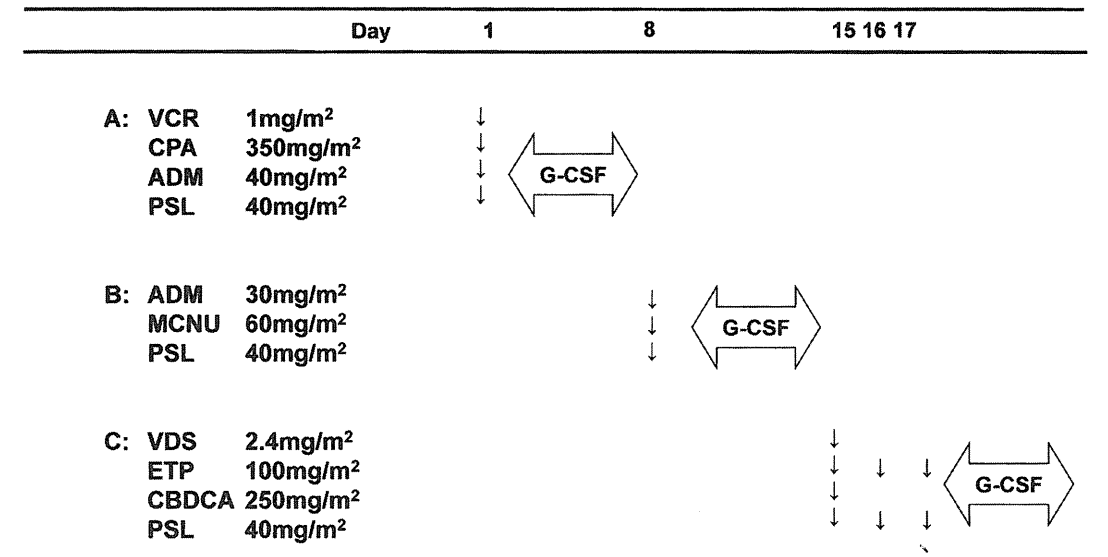

Fig. 8.3 Regimen of VCAP-AMP-VECP. Ranimustinal (MCNU) and vindesine (VDS) are nitrosourea and vinca alkaloid, respectively, developed in Japan. A previous study on myeloma described that carmustine (BCNU), another nitrosourea, at 1 mg/kg is equivalent to MCNU at 0.8–1.0 mg/kg. VDS at 2.4 mg/m^2 can be substituted for VCR, another vinca alkaloid used in this regimen, at 1 mg/m^2 with possibly less myelosuppression and more peripheral neuropathy which can be managed by dose modification. VCAP=vincristine (VCR), cyclophosphamide (CPA), doxorubicin (ADM), prednisone (PSL); AMP=ADM, MCNU, PSL; VECP=VDS, etoposide (ETP), carboplatin (CBDCA) and PSL. [Based on data from Tsukasaki K, Utsunomiya A, Fukuda H, et al.: VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 25:5,458–5,564, 2007.]

prophylactic intrathecal administration, at the recovery phases of courses 1, 3, and 5 because of the high frequency of central nervous system relapse in the JCOG9303 study. Untreated patients with aggressive ATL were assigned to receive either six courses of LSG15 every 4 weeks or eight courses of biweekly CHOP. The primary endpoint was overall survival. A total of 118 patients were enrolled. The CR rate was higher in the LSG15 arm than in the biweekly CHOP arm (40% vs. 25%, respectively; $P=0.020$). As illustrated in Figure 8.4, the median survival time and OS rate at 3 years were 12.7 months and 24% in the LSG15 arm and 10.9 months and 13% in the biweekly CHOP arm [two-sided $P=0.169$, and the hazard ratio was 0.75; 95% confidence interval (CI), 0.50 10 1.13]. A Cox regression analysis with performance status (PS 0 vs. 1 vs. 2–4) as the stratum for baseline hazard functions was performed to evaluate the effect on overall survival of age, B-symptoms, subtypes of ATL, LDH, BUN, bulky mass, and treatment arms. According to this analysis, the hazard ratio and two-sided P value for the treatment arms were 0.62 (95% CI, 0.38–1.01) and 0.056, respectively. The difference between the crude analysis and this result was because of unbalanced prognostic factors, such as PS 0 vs. 1, and the presence or absence of bulky lesions between the treatment arms. The progression-free survival rate at 1 year was 28% in the LSG15 arm compared with 16% in the biweekly CHOP arm (two-sided $P=0.200$).

In VCAP-AMP-VECP vs. biweekly CHOP, rate of grade 4 neutropenia, grade 4 thrombocytopenia, and grade 3/4 infection were 98% vs. 83%, 74% vs. 17%, and 32% vs. 15%, respectively. There were three toxic deaths in the former. Three treatment-related deaths (TRDs), two from sepsis and one from interstitial pneumonitis

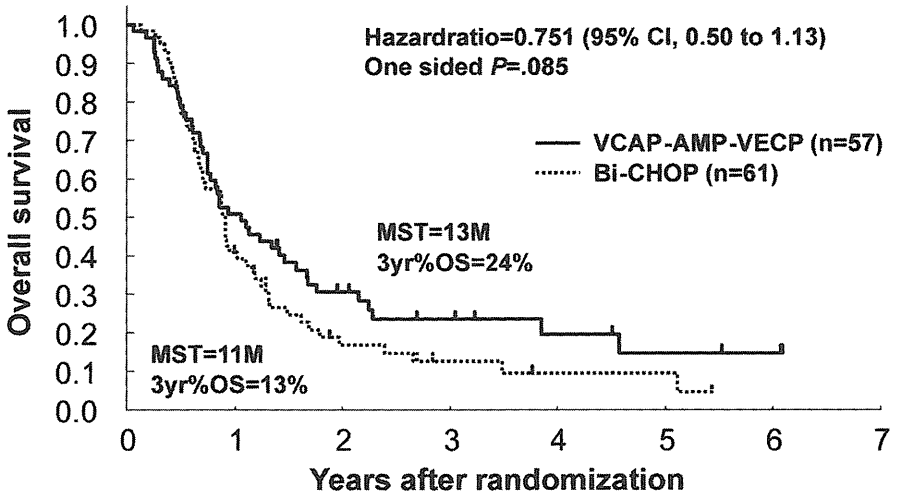

Fig. 8.4 Kaplan-Meier Estimate of Overall Survival for all Randomly Assigned Patients in JCOG9801. CI = confidential interval; VCAP = vincristine, cyclophosphamide, doxorubicin, prednisone; AMP = doxorubicin, ranimustine, prednisone; VECP = vindesine, etoposide, carboplatin, prednisone; MST = median survival time; OS = overall survival; [Based on data from Tsukasaki K, Utsunomiya A, Fukuda H, et al.: VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 25:5,458–5,564, 2007.]

related to neutropenia, were reported in the VCAP-AMP-VECP arm. Two cases of myelodysplastic syndrome were reported, one each in both arms.

The longer survival at 3 years and higher CR rate with LSG15 compared with biweekly CHOP suggest that LSG15 is a more effective regimen at the expense of higher toxicity, providing the basis for future investigations in the treatment of ATL [107]. The superiority of VCAP-AMP-VECP to biweekly CHOP may be explained by the more prolonged, dose dense schedule of therapy in addition to four more drugs. In addition, agents such as carboplatin and ranimustine not affected by multidrug-resistance related genes, which were frequently expressed in ATL cells at onset, were incorporated [109]. Intrathecal prophylaxis, which was incorporated in both arms of the phase III study, should be considered for patients with aggressive ATL even in the absence of clinical symptoms because a previous analysis revealed that more than half of relapses at new sites after chemotherapy occurred in the CNS [110]. However, the median survival time of 13 months still compares unfavorably to other hematological malignancies, requiring further effort to improve the outcome.

Interferon-Alpha and Zidovudine

A small phase II trial in Japan of IFN alpha against relapsed/refractory ATL showed a response rate (all PR) of 33% (8/24), including five out of nine (56%) chronic type ATL [111]. In 1995, Gill and associates reported that 11 of 19 patients with acute- or lymphoma-type ATL showed major responses (five CR and six PR) to a combination of interferon-alpha (IFN) and zidovudine (AZT) [112]. The efficacy of this combination was also observed in a French study; major objective responses were obtained in all five patients with ATL (four with acute type and one with smoldering type) [113]. Although these results are encouraging, the OS of previously untreated patients with ATL was relatively short (4.8 months) compared with the survival of those in the chemotherapy trials conducted by the JCOG-LSG (7–8 months) [114]. After that, numerous small phase II studies using AZT and IFN have shown responses in ATL patients [115–117]. High doses of both agents are recommended: 6–9 million units of IFN in combination with daily divided AZT doses of 800–1,000 mg/day.

Recently, the results of a "meta-analysis" on the use of IFN and AZT for ATL were reported

[118]. A total of 100 patients received interferon-alpha and AZT as initial treatments. The ORR was 66%, with a 43% CR rate. In this worldwide retrospective analysis, the median survival time was 24 months and the 5-year survival rate was 50% for first-line IFN and AZT, vs. 7 months and 20% for 84 patients who received first-line chemotherapy. The median survival time of patients with acute-type ATL treated with first-line IFN/AZT and chemotherapy was 12 and 9 months, respectively. Patients with lymphoma-type ATL did not benefit from this combination. In addition, first-line IFN/AZT therapy in chronic- and smoldering-type ATL resulted in a 100% survival rate at a median follow-up of 5 years. While the results for IFN/AZT in indolent ATL appear to be promising compared to those with watchful-waiting policy until disease progression, recently reported from Japan [101], the possibility of selection bias cannot be ruled out. A prospective multicenter phase III study evaluating the efficacy of IFN/AZT as compared to watchful-waiting for indolent ATL is to be initiated in Japan.

Recently, a phase II study of the combination of arsenic trioxide, IFN, and AZT for chronic ATL revealed an impressive response rate and moderate toxicity [119]. Although the results appeared promising, the addition of arsenic trioxide to IFN/AZT, which might be sufficient for the treatment of chronic ATL as described above, caused more toxicity and should be evaluated with caution.

Allergenic Hematopoietic Stem-Cell Transplantation (allo-HSCT)

Allo-HSCT is now recommended for the treatment of young patients with aggressive ATL. Despite higher treatment-related mortality in a retrospective multicenter analysis of myeloablative allo-HSCT, the estimated 3-year OS of 33% is promising, possibly reflecting a graft versus ATL effect [120]. To evaluate the efficacy of allo-HSCT more accurately, especially in view of a comparison with intensive chemotherapy, a prospective multicenter phase II study of LSG15 chemotherapy followed by allo-HSCT will be initiated in Japan.

Feasibility studies of allo-HSCT with reduced intensity conditioning for ATL also revealed promising results, and a subsequent multicenter trial of RIST is being conducted in Japan [121, 122]. The minimal residual disease after allo-HSCT detected as HTLV-1 proviral load was much less extensive than that after chemotherapy or AZT/IFN therapy, suggesting the presence of a graft-versus-ATL effect as well as graft-versus-HTLV-1 activity [121]. It remains unclear which type of allo-HSCT (myeloablative or reduced intensity conditioning) is more suitable for the treatment of ATL. Furthermore, selection criteria with respect to responses to previous treatments, sources of stem cells, and HTLV-1 viral status of the donor remain to be determined. However, several other retrospective studies as well as those mentioned above on allo-HSCT showed a promising long-term survival rate of 20–40% with an apparent plateau phase despite significant treatment-related mortality.

Supportive Care

The prevention of opportunistic infections is essential in the management of ATL patients, nearly half of whom develop severe infections during chemotherapy. Some patients with indolent ATL develop infections during watchful waiting. Sulfamethoxazole/trimethoprim and antifungal agents have been recommended as prophylaxes for Pneumocystis jiroveci pneumonia and fungal infections, respectively, in the JCOG trials [105–107]. While cytomegalovirus infections are not infrequent among ATL patients, ganciclovir is not usually recommended as a prophylaxis [55]. In addition, in patients not receiving chemotherapy, antifungal prophylaxis may not be critical. An anti-strongyloides agent, such as ivermectin or albendazole, should be considered to avoid systemic infections in patients with a history of exposure to the parasite in the tropics. Treatment with steroids and proton pump inhibitors may precipitate a fulminant strongyloides infestation and warrants testing before these agents are used in endemic areas [55]. Hypercalcemia associated with aggressive ATL can be corrected using chemotherapy in

combination with hydration and bisphosphonate even when the PS of the patient is poor.

Response Criteria in ATL

The complex nature of ATL, often with both leukemic and lymphomatous components, makes response assessment difficult. A modification of the JCOG response criteria was suggested reflecting those for CLL and NHL which had been published later [55, 123, 124]. Recently, revised response criteria were proposed for lymphoma, incorporating positron emission tomography (PET), especially for the assessment of CR. It is well known and described in the criteria that several kinds of lymphoma including PTCLs were variably [18F]fluorodeoxyglucose avid [125]. Meanwhile, PET or PET/CT is recommended for evaluations of response for ATL when the tumorous lesions are FDG-avid at diagnosis [57].

New Agents for ATL

Topoisomerase Inhibitors

MST-16, a new orally administered bis(2,6-dioxopiperazine) analogue and an inhibitor of topoisomerase II, showed some activity with little cross resistance toward lymphoid malignancies in vitro and in vivo. MST-16 at 1,200–2,800 mg/day was given orally daily for 7 days, with courses repeated at intervals of 2–3 weeks to 24 patients with ATL in a phase I–II study [126]. Two CRs and eight PRs were obtained in 23 (13 acute, 8 lymphoma, and 2 chronic ATL) evaluable patients. Remissions were obtained at 7–232 (median, 23) days and lasted 43–374 (median, 68) days. The major toxic effects were leukopenia (68%), anemia (52%), thrombocytopenia (35%), and gastrointestinal disorders (22%). Although this agent showed promising activity against ATL as a single agent, no further study in combination with other agents has been reported.

Irinotecan hydrochloride (CPT-11) is a semisynthetic camptothecin with inhibitory activity against topoisomerase I. Preclinical studies of CPT-11 have suggested a lack of cross-resistance between topoisomerase I inhibitors and other anticancer agents. Multicenter phase II studies of CPT-11 have been conducted against relapsed or refractory NHL [127]. In this study, 9 patients achieved a CR, and 17 patients achieved a PR (response rate 38%: 26 of 69), using a weekly intravenous administration of 40 mg/m^2/day for three consecutive days. Within this group, 5 of 13 patients with ATL (38%) responded to CPT-11 (one CR and four PR) [127]. The major toxic effects of CPT-11 were leukopenia, diarrhea, and nausea and/or vomiting. Subsequently, to develop a new chemo therapy regimen effective against NHL and ATL, two kinds of phase I/II studies of CPT-11 in combination with CBDCA or ETP were conducted for relapsed or refractory NHL. In both studies, however, dose escalation was halted because of hematologic toxicity (in combination with CBDCA) and hepatotoxicity (in combination with ETP).

Purine Analogs

Several purine analogs have been evaluated for ATL. Among them, pentostatin (deoxycoformycin) has been most extensively evaluated as a single agent and in combination as described above [105, 108]. Other purine analogs clinically studied for ATL are fludarabine and cladribine. Fludarabine is among standard treatments for B-chronic lymphocytic leukemia and other lymphoid malignancies. In a phase I study of fludarabine in Japan, five ATL patients and ten B-CLL patients with refractory or relapsed-disease were enrolled [128]. Six grade 3 non-hematological toxicities were only observed in the ATL patients. PR was achieved only in one of the five ATL patients and the duration was short. Cladribine is among standard treatments for hairy cell leukemia and other lymphoid malignancies. A phase II study of cladribine for relapsed/refractory aggressive-ATL in 15 patients revealed only one PR [129].

Forodesine, a purine nucleotide phosphorylase (PNP) inhibitor, is among purine nucleotide

analogs. PNP is an enzyme in the purine salvage pathway that phosphorolysis 2'deoxyguanosine (dGuo). PNP deficiency in humans results in a severe combined immunodeficiency phenotype and the selective depletion of T cells associated with high plasma deoxyguanosine (dGuo) and high intracellular deoxyguanosine triphosphate levels in those cells with high deoxynucleoside kinase activity such as T cells, leading to cell death. Inhibitors of PNP, such as forodesine, mimic SCID in vitro and in vivo, suggesting a new targeting agent specific for T-cell malignancies [130]. A dose escalating phase I study of forodesine is being conducted for T-cell malignancies including ATL.

Histone Deacetylase Inhibitors

Gene expression governed by epigenetic changes is crucial to the pathogenesis of cancer. Histone deacetylases (HDACs) are enzymes involved in the remodeling of chromatin and play a key role in the epigenetic regulation of gene expression. Deacetylase inhibitors (DACi) induce the hyperacetylation of non-histone proteins as well as nucleosomal histones resulting in the expression of repressed genes involved in growth arrest, terminal differentiation, and/or apoptosis among cancer cells. Several classes of HDACi have been found to have potent anticancer effects in preclinical studies. HDACis such as vorinostat (suberoylanilide hydroxamic acid), romidepsin (depsipeptide), and panobinostat (LBH589) have also shown promise in preclinical and/or clinical studies against T-cell malignancies including ATL [131]. Vorinostat and romidepsin have been approved for cutaneous T-cell lymphoma (CTCL) by the Food and Drug Administration in the USA. LBH589 has a significant anti-ATL effect in vitro and in mice [132]. However, a phase II study for CTCL and indolent ATL was terminated because of severe infections associated with the shrinkage of skin tumors and formation of ulcers in patients with ATL. Further study is required to evaluate the efficacy of HDACIs for PTCL/CTCL including ATL.

Monoclonal Antibodies and Toxin Fusion Proteins

Monoclonal antibodies (MoAb) and toxin fusion proteins targeting several molecules expressed on the surface of ATL cells and other lymphoid malignant cells, such as CD25, CD2, CD52 and CCR4, have shown promise in recent clinical trials. Because most ATL cells express the alpha-chain of IL-2R (CD25), Waldmann et al. treated patients with ATL using monoclonal antibodies to CD25 [133]. Six (32%) of 19 patients treated with anti-Tac showed objective responses lasting from 9 weeks to longer than 3 years. One impediment to this approach is the quantity of soluble IL-2R shed by the tumor cells into the circulation. Another strategy for targeting IL-2R is conjugation with an immunotoxin (Pseudomonas exotoxin) or radioisotope (yttrium-90). Waldmann et al. developed a stable conjugate of anti-Tac with yttrium-90. Among the 16 patients with ATL who received 5- to 15-mCi doses, 9 (56%) showed objective responses. The response lasted longer than that obtained with unconjugated anti-Tac antibody [134, 135].

LMB-2, composed of the anti-CD25 murine MoAb fused to the truncated form of Pseudomonas toxin, was cytotoxic to CD25-expressing cells including ATL cells in vitro and in mice. Phase I/II trials of this agent showed some effect against hairy cell leukemia, CTCL, and ATL [136]. Six of thirty-five patients in the phase I study had significant levels of neutralizing antibodies after the first cycle. This drug deserves further clinical trials including in combination with cytotoxic agents.

Denileukin diftitox (DD; DAB(389)-interleukin-2 [IL-2]), an interleukin-2-diphtheria toxin fusion protein targeting IL-2 receptor-expressing malignant T lymphocytes, shows efficacy as a single agent against CTCL and PTCL [137]. Also, the combination of this agent with multi-agent chemotherapy, CHOP, was promising for PTCL [138]. ATL cells frequently and highly express CD25 as described above and several ATL cases successfully treated with this agent have been reported [139].

CD52 antigen is present on normal and pathologic B and T cells. In PTCL, however, CD52

expression varies among patients, with an overall expression rate lower than 50% in one study but not in another [140, 141]. ATL cells frequently express CD52 as compared to other PTCLs. The humanized anti-CD52 monoclonal antibody alemtuzumab is active against CLL and PTCL as a single agent. The combination of alemtuzumab with a standard-dose cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) regimen as a first-line treatment for 24 patients with PTCL showed promising results with CR in 17 (71%) patients, 1 had a partial remission, with an overall median duration of response of 11 months and was associated with mostly manageable infections but including CMV reactivation [142]. Major infections were Jacob–Creutzfeldt virus reactivation, pulmonary invasive aspergillosis, and Staphylococcus sepsis.

ATL cells express CD52, the target of alemtuzumab, which was active in a preclinical model of ATL and toxic to p53-deficient cells, and several ATL cases successfully treated with this agent have been reported [143–145].

Siplizumab is a humanized MoAb targeting CD2 and showed efficacy in a murine ATL model. P1 dose-escalating study of this agent in 22 patients with several kinds of T/NK-cell malignancy revealed six responses (two CR in LGL leukemia, three PR in ATL and one PR in CTCL). However, four patients developed EBV-associated LPD [146]. The broad specificity of this agent may eliminate both CD4- and CD8-positive T cells as well as NK cells without affecting B cells and predispose individuals to the development of EBV lymphoproliferative syndrome.

CCR4 is expressed on normal T helper type 27 and regulatory T (Treg) cells and on certain types of T-cell neoplasms [63, 94]. KW-0761, a next generation humanized anti-CCR4 mAb, with a defucosylated Fc region, exerts strong antibody-dependent cellular cytotoxicity due to increased binding to the Fcγ receptor on effecter cells [147]. A phase I study of dose escalation with four weekly intravenous infusions of KW-0761 in 16 patients with relapsed CCR4-positive T-cell malignancy (13 ATL and 3 PTCL) revealed that one patient, at the maximum dose (1.0 mg/kg), developed grade (G) three dose-limiting toxic effects, namely skin rashes and febrile neutropenia, and G4 neutropenia [148]. Other treatment-related G3-4 toxic effects were lymphopenia ($n=10$), neutropenia ($n=3$), leukopenia ($n=2$), herpes zoster ($n=1$), and acute infusion reaction/cytokine release syndrome ($n=1$). Neither the frequency nor severity of these effects increased with dose escalation or the plasma concentration of the agent. The maximum tolerated dose was not reached. No patients had detectable levels of anti-KW-0761 antibody. Five patients (31%; 95% CI, 11–59%) achieved objective responses: two complete (0.1; 1.0 mg/kg) and three partial (0.01; 2 at 1.0 mg/kg) responses. Three out of thirteen patients with ATL (31%) achieved a response (two CR and one PR). Responses in each lesion were diverse, that is, good in PB (six CR and one PR/seven evaluable cases), intermediate in skin (three CR and one PR/eight evaluable cases), and poor in LN (1 CR and 2 PR/11 evaluable cases). KW-0761 was well tolerated at all the doses tested, demonstrating potential efficacy against relapsed CCR4-positive ATL or PTCL. Recently, results of subsequent phase II studies at the 1.0 mg/kg in relapsed ATL, showing 50% of response rate with acceptable toxicity profiles, were reported [149]. Also, a phase II trial of single agent KW-0761 at the 1.0 mg/kg in relapsed PTCL/CTCL and a phase II trial of VCAP-AMP-VECP combined with KW-0761 for untreated aggressive ATL are ongoing.

Other Novel Agents

Pralatrexate (Folotyn) is a new agent with potent preclinical and clinical activity in T-cell malignancies including ATL [150–152]. The agent is a novel anti-folate with improved membrane transport and polyglutamylation in tumor cells and high affinity for the reduced folate carrier highly expressed in malignant cells. Other potential drugs for ATL under investigation include a proteasome inhibitor, bortezomib (Velcade), and an immunomodulatory agent, lenalidomide (Revlimid) [153–155].

Table 8.3 Strategy for the treatment of Adult T-Cell Leukemia-Lymphoma

Smoldering- or favorable chronic-type ATL
• Consider inclusion in
• Symptomatic patients (skin lesions, opportunistic infections, etc.): Consider AZT/IFN or Watch and Wait
• Asymptomatic patients: Consider Watch and Wait
Unfavorable chronic- or acute-type ATL
• If outside clinical trials, check prognostic factors (including clinical and molecular factors if possible):
– Good prognostic factors: consider chemotherapy (VCAP-AMP-VECP evaluated by a phase III trial against biweekly-CHOP) or AZT/IFN (evaluated by a meta-analysis on retrospective studies)
– Poor prognostic factors: consider chemotherapy followed by conventional or reduced intensity allo-HSCT (evaluated by retrospective and prospective Japanese analyses, respectively).
– Poor response to initial therapy: Consider conventional or reduced intensity allo-HSCT
Lymphoma-type ATL
• If outside clinical trials, consider chemotherapy (VCAP-AMP-VECP)
• Check prognostic factors (including clinical and molecular factors if possible) and response to chemotherapy:
– Good prognostic factors and good response to initial therapy: Consider chemotherapy followed by observation
– Poor prognostic factors or poor response to initial therapy: Consider chemotherapy followed by conventional or reduced intensity allo-HSCT

[Based on data from Tsukasaki K, Hermine O, Bazarbachi A, et al.: Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: A proposal from an international consensus meeting. J Clin Oncol 27:453–459, 2009.]

Prevention of ATL

Two steps should be considered for the prevention of HTLV-1-associated ATL. The first is the prevention of HTLV-1 infections. This has been achieved in some endemic areas in Japan by screening for HTLV-1 among blood donors and asking mothers who are carriers to refrain from breast feeding. The second step is the prevention of ATL among HTLV-1 carriers. This has not been achieved partly because only about 5% of HTLV-1 carriers develop the disease in their life time, although several risk factors have been identified by a cohort study of HTLV-1 carriers (Joint Study of Predisposing Factors for ATL Development) [83]. Also, no agent has been found to be effective in preventing the development of ATL among HTLV-1 carriers.

Ongoing Clinical Trials

Clinical trials have been paramount to the recent advances in ATL treatment, including assessments of chemotherapy, AZT/IFN, and allo-HSCT. Recently, a strategy for ATL treatment, stratified by subclassification, prognostic factors, and the response to initial treatment as well as response criteria was proposed (Table 8.3) [57]. The recommended treatment algorithm for ATL is shown in Fig. 8.2. However, as described in this chapter, ATL still has a worse prognosis than the other T-cell malignancies [156]. There is no plateau with an initial steep slope and subsequent gentle slope without a plateau in the survival curve for aggressive or indolent ATL treated by watchful waiting and with chemotherapy, respectively, although the prognosis is much better in the latter [14, 61]. A prognostic model for each subgroup should be elucidated to properly identify the candidate for allo-HSCT which can achieve a cure of ATL despite considerable treatment-related mortality. Although several small phase II trials suggested IFN/AZT therapy to be promising, no confirmative phase III study has been conducted. Furthermore, as described in the other chapters in detail, more than ten promising new agents for PTCL/CTCL including ATL are now in clinical trials or preparation. Future clinical trials on ATL as described above should be incorporated to ensure that the strategy as shown in Table 8.3 is continually updated to establish evidence-based practical guidelines.

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2) フルダラ注　20 mg/m² 30分かけて点滴静注　5日間　4週ごとに繰り返す
3) エンドキサン錠（50 mg）　1-2錠　分1　朝食後　連日
4) リツキサン注　1回375 mg/m²　週1回　点滴静注　4回 保外

フルダラは腎機能低下例（クレアチニンクリアランス70 mL/分以下）に対して減量基準があるため，それに応じた適正量を投与する．骨髄抑制が遷延することがあるため，投与量を適宜減量する．フルダラ経口投与の場合，悪心・嘔吐など消化器症状の出現頻度が高いため，5-HT_3受容体拮抗薬など制吐薬内服も併用する．

リツキサン投与に際しては輸注関連毒性に注意が必要であり，抗ヒスタミン薬と解熱鎮痛薬の予防投与を行う．さらに初回投与は25 mg/時から開始し，1時間投与し異常がなければ，100 mg/時に増量する．さらに1時間投与し異常がなければ，200 mg/時に増量し最後まで投与する．

Ⓑ HCL

HCLはクラドリビン（ロイスタチン）が有効であり，1コースの治療により寛解が得られることが多い．

Ⓡ 処方例
ロイスタチン注　1日0.09 mg/kg　持続点滴静注　7日間

Ⓒ 感染症

フルダラビンやクラドリビンなどのプリンアナログを長期投与する際にはCD4陽性T細胞減少による重症日和見感染に注意する．ニューモシスチス肺炎の予防のためST合剤の予防内服が推奨される．カンジダなどの真菌感染症や帯状疱疹，サイトメガロウイルスなどのウイルス感染症にも注意が必要である．

服薬指導・薬剤情報　三輪一智

- フルダラ静注用およびフルダラ錠は，重篤な腎障害のある患者（クレアチニンクリアランス30 mL/分未満）に対し禁忌である．腎機能低下患者（クレアチニンクリアランス30-70 mL/分）では，添付文書などの減量目安を参考に，安全性を確認しながら慎重に投与する．重篤な副作用として骨髄抑制，遷延性のリンパ球減少があり，患者には日頃から感染予防に努めるよう注意するとともに，発熱，発疹，咽頭痛，全身倦怠感の症状が現れた際はすみやかに申し出るよう指導する．
- リツキサン注は抗ヒスタミン薬，解熱鎮痛薬などの前投与を行った患者においてもinfusion reaction（発熱，悪寒，頭痛など）が起こることがある．特に初回投与時，投与開始24時間以内に高頻度に発現するので注意する．
- フルダラ，リツキサン注の両剤ともに，B型肝炎ウイルスキャリアの患者で劇症肝炎や肝炎の増悪を引き起こすことがあるので，継続した肝機能検査，肝炎ウイルスマーカーのモニタリングを要する．

成人T細胞白血病・リンパ腫
adult T-cell leukemia-lymphoma（ATL）

塚崎邦弘　国立がん研究センター東病院・血液腫瘍科科長

病態と診断

成人T細胞白血病・リンパ腫（ATL）は，レトロウイルスのhuman T-lymphotropic virus type I（HTLV-1）が染色体DNAにプロウイルスとして単クローン性に組み込まれている成熟T細胞白血病・リンパ腫であり，HTLV-1のendemic area（西南日本沿岸地域，中南米，アフリカなど）出身の成人（日本での発症年齢の中央値は67歳，30歳未満での発症はまれ）に好発する．

リンパ節腫脹，肝脾腫，皮膚浸潤が多く，消化管，肺，腎，中枢神経，骨などに浸潤する場合もある．よく合併する高Ca血症や日和見感染症がさらに症状を多彩にする．くすぶり型や慢性型は，検診などで末梢血液像異常により発見される場合も多い．白血化した急性型，慢性型，くすぶり型では末梢血に，リンパ腫型ではリンパ節に，花弁状の核をもつATLL細胞を認める．血清LDH，Caや可溶性IL-2受容体はATLLの病勢を示すよいマーカーである．抗HTLV-1抗体が陽性であり，ATLL細胞は活性化した成熟Th2/制御性T細胞の表面形質（$CD3^+$，$CD4^+$，$CD8^-$，$CD25^+$，$CCR4^+$，$FoxP3^+$，$FoxP3^-$，TdT^-）を有する．以上より典型例の診断は容易である．非典型例では，ATLL細胞DNAにHTLV-1遺伝子の単クローン性組み込みを証明して確定診断する．

予後因子としては，年齢，全身状態（PS：performance status），総病変数，高Ca血症，高LDH血症が重要である．予後因子解析と臨床病態の特徴から，白血化，臓器浸潤，高LDH血症，高Ca血症の有無と程度により病型分類が提唱され，生存期間中央値は急性型6か月，リンパ腫型10か月，慢性型24か月，くすぶり型では3年以上であった．

表　VCAP－AMP－VECP 療法

			診療日
			① 2 3 4 5 6 7 ⑧ 9 10 11 12 13 14 ⑮ ⑯ ⑰ 18 19 20 － 27 28
A) VCAP	(mg/m^2)		
オンコビン注（VCR）	1	静注	○
エンドキサン注（CPA）	350	点滴	○
アドリアシン注（ADR）	40	点滴	○
プレドニン錠（PSL）	40	経口	○
B) AMP			
アドリアシン注（ADR）	30	点滴	○
サイメリン注（MCNU）	60	点滴	○
プレドニン錠（PSL）	40	経口	○
C) VECP			
フィルデシン注（VDS）	2.4	静注	○
ベプシド注（ETP）	100	点滴	○○○
パラプラチン注（CBDCA）	250	点滴	○
プレドニン錠（PSL）	40	経口	○○○
G－CSF		皮下注	○○○○○　○○○○○　○○○－○

オンコビンは最大量 2 mg まで使用．好中球数 1,000/μL 以下のとき，G－CSF を開始して 5,000/μL 以上へ回復するまで連日使用する．B)と C)は好中球 500/μL 以上で，次の A)は好中球 1,000/μL 以上で開始する．A)，B)，C)の順に 28 日を 1 コースとして計 6 コース施行する．29 日目から次期コース開始．1，3，5 コース後，血小板 7 万/μL 以上を確認して，メソトレキセート 15 mg を注射用水 3 mL に溶解して，キロサイド 40 mg，水溶性プレドニン 10 mg とともに髄注する．

治療方針

急性型やリンパ腫型は CHOP 療法などに抵抗性であるため，G－CSF を併用して短い治療間隔で強力な化学療法を繰り返す．また，しばしば中枢神経系に再発するため予防的に髄注を併用する．

慢性型やくすぶり型 ATLL の治療法は，急性転化するまでは watchful waiting が原則とされるがその長期予後は良好ではない．

同種造血幹細胞移植療法は，有害反応は強いが，宿主片対 ATL 効果により長期生存が期待できる．ドナー，移植の前処置法など症例の選択規準は確立していないが，積極的に検討すべき治療法である．

合併症対策としては，高 Ca 血症の治療と日和見感染症の予防/治療が重要である．

Ⓐ watchful waiting・化学療法・移植療法・分子標的療法

1. くすぶり型/慢性型　無治療でも長期生存が期待できる，くすぶり型や予後不良因子（血清 LDH，BUN，アルブミンのいずれかが異常）を有さない慢性型 ATLL は，急性転化などの病勢悪化があるまで積極的な治療の対象ではない（watchful waiting）．好発する皮膚病変には局所的治療として副腎皮質ステロイド外用または紫外線療法を行う．

予後不良因子を有する慢性型は生存期間中央値が 15 か月と不良なため，下記の治療を検討する．

2. 急性型/リンパ腫型

a. VCAP－AMP－VECP 療法　biweekly CHOP 療法よりも完全寛解率と生存割合で上回っていた，mLSG 15（VCAP－AMP－VECP）療法を用いる（表）．化学療法後の汎血球減少症には，下記の感染対策と赤血球・血小板輸血を行う．

高齢者に対する治療法は確立しておらず，上記の治療法を減量して行われている．

b. VCAP－AMP－VECP 療法後に難治または再発で移植の適応もない場合

1 ATL 細胞が CCR 4 陽性の場合　再発した急性型，リンパ腫型または予後不良因子を有する慢性型に 50％の奏効割合を示したヒト化抗 CCR 4 抗体のポテリジオを用いる．急性輸液反応予防の所定の対処のほか，有害反応の発疹には，ステロイド内服などで対処する．

℞ 処方例

ポテリジオ注　1 回 1 mg/kg　1 週間間隔で 8 回　点滴静注

2 ATL 細胞が CCR 4 陰性かポテリジオが無効の場合

℞ 処方例　下記を併用する．

カンプト注　1 回 30 mg/m^2　1 日 1 回　点滴静注　3 日間

ランダ注　1 回 15 mg/m^2　1 日 1 回　点滴静注

3日間

Ⓑ 合併症対策

1. 高Ca血症の治療　急性型/リンパ腫型ではしばしば高度の高Ca血症を生じる．高Ca血症により全身状態が不良であっても，前述の抗癌剤に下記治療を併用することにより，Ca値はすみやかに正常化することが多い．

℞ 処方例　下記を適宜組み合わせて用いる．

1) アレディア注　1回30－45 mg　4時間以上かけて点滴静注，またはゾメタ注　1回4 mg　15分以上かけて点滴静注　その後少なくとも1週間休薬
2) エルシトニン注（40単位）　1回40単位　1日2回　筋注または点滴静注
3) 生理食塩液　1,000 mL＋7%メイロン注　20 mL　1日2－3回　点滴静注
4) ラシックス注（20 mg）　1回20 mg　1日1－3回　静注 22

2. 感染症の予防と治療　エイズ同様に，ニューモシスチス肺炎，真菌症，結核，サイトメガロウイルス感染症などがしばしば起こる．日和見感染症は病原体が同定されなくても，臨床・画像的特徴などにより経験的に治療を早期に開始することにより救命できる場合も多い．これらは化学療法後やATLLの増悪期に合併しやすく，しばしば致死的となるので，以下の予防を行う．

a. 好中球数が1,000/μL以下の場合　感染症の予防のためG－CSFを使用する．

℞ 処方例　下記のいずれかを用いる．

1) グラン注　1回75 μg　1日1回　皮下注　連日
2) ノイトロジン注　1回100 μg　1日1回　皮下注　連日

b. 真菌感染症予防

℞ 処方例　下記のいずれかを用いる．

1) ジフルカンカプセル（100 mg）　1カプセル　分1　朝食後　連日 保外
2) イトリゾールカプセル（50 mg）　2カプセル　分1　朝食後　連日 保外 48

c. ニューモシスチス肺炎予防

バクタ配合錠　1錠　分1　朝食後　連日 47

d. 結核の既往のある患者

イスコチン錠（100 mg）　3錠　分1　朝食後　連日 保外

e. 上記感染症を合併した場合　強力な治療が必要である．細菌やウイルス（特にサイトメガロ）感染症に対する，早期からの的確な治療も重要である．

患者説明のポイント

- 内服薬による感染予防の意義を説明する．
- 病状悪化時の臓器腫大や高Ca血症による症状，日和見感染症の症状を説明する．
- HTLV－1に関しての質問があれば，感染予防が可能であること，HTLV－1キャリアにおけるATLL発症予防法は確立していないがその生涯での頻度は数%と高くないことを説明する．

ホジキンリンパ腫
Hodgkin lymphoma（Hodgkin's disease）

伊豆津宏二　虎の門病院・血液内科部長（東京）

病態と診断

Ⓐ 病態

ホジキンリンパ腫（HL）では，リンパ節や縦隔などが主な病変部位となる．古典的HL（さらに結節硬化，混合細胞，リンパ球豊富，リンパ球減少の4病型に分類される）と結節性リンパ球優位型HLに大別されるが，後者はまれである．

Ⓑ 診断

古典的HLでは病理組織学的に反応性のリンパ球を背景として大型腫瘍細胞（リード－ステルンベルグ細胞，ホジキン細胞）が散在性に認められる．これらは多くの場合CD 30陽性，CD 15陽性，Pax 5陽性で，一部はCD 20陽性である．エプスタイン－バーウイルス（EBV）陽性の場合には加齢性EBV陽性B細胞リンパ増殖性疾患などとの鑑別が問題となる．

治療方針

診察と胸部－骨盤部の造影CT（診察上，頭頸部に病変がある場合には頸部も），PET/CT，骨髄生検により臨床病期を把握し，治療方針を決定する．

診断時，半数以上の患者が限局期（I，II期）である．ドイツHL研究グループ（GHSG）では限局期HLで巨大病変，節外病変，血沈亢進，病変リンパ節領域数3以上のいずれかがある場合に予後不良因子ありと定義している．

一方，進行期HL（III，IV期）では年齢45歳以上，男性，IV期，ヘモグロビン10.5 g/dL未満，血清アルブミン4 g/dL未満，リンパ球数600/μLまたは白血球の8%未満，白血球数15,000/μL以上を予後不良因子とし，その数により国際予後スコア（IPS）が規定されている．

Ⓐ 限局期

ABVD療法と局所放射線療法（IFRT）の併用療法が標準的治療である．予後不良因子のない限局期

8 成人T細胞白血病・リンパ腫 (adult T-cell leukemia-lymphoma : ATL)

◆ 総論

成人T細胞白血病・リンパ腫（adult T-cell leukemia-lymphoma：ATL）は，九州・沖縄地方を主とする西南日本に多発するT細胞腫瘍として，1977年内山，高月らによって提唱された疾患概念である[1]。1980年代のはじめには原因ウイルスとしてhuman T-lymphotropic virus type-I（HTLV-1）が発見された[2)~5)]。WHO分類（2008）においてATLは，高度の核異型を伴ったリンパ球よりなる，HTLV-1によって引き起こされる末梢性T細胞腫瘍と定義されている[6]。

Flower cellと呼ばれる異常リンパ球の増多を主体とした白血球増多，リンパ節腫脹，皮膚病変，ATL細胞の浸潤による多臓器障害，高LDH血症，高Ca血症，日和見感染症などが出現する。日本以外では中央アフリカおよび中南米出身者に比較的高頻度に発生している。HTLV-1キャリアは現在日本には西南日本沿岸部を主に110万人程度存在し，キャリアからATLの発症率は年間1,000人に0.6~0.7人とされる[7)8)]。HTLV-1の感染は感染細胞が正常リンパ球に直接接触して成立する。感染経路として輸血，性交，母乳が知られているが，ATL発症につながる重要な感染経路は母乳である。いくつかの多発地域ではHTLV-1母子感染予防対策が行われており，6カ月以上の長期授乳による母子感染率は20.5%であるのに対して人工栄養による母子感染率は2.4%と報告されている[9]。

ATL発症は20歳代までは極めて稀で，その後増加し，60歳頃をピークにして以降徐々に減少する。1人のHTLV-1キャリアが，生涯でATLを発症する確率は約5%である。HTLV-1キャリアにおけるATL発症の危険因子としては，多変量解析で，母子感染，高齢者，末梢血中の高ウイルス量，ATLの家族歴あり，他の疾患の治療中に初めて抗HTLV-1抗体検査を受け陽性が判明した症例[10]が報告されている。近年，HTLV-1キャリアとATL患者の高齢化が進んでいる[11)12)]。

1991年にJapan Clinical Oncology Group（JCOG）リンパ腫グループ（LSG）による813例のATL患者の全国実態調査をもとに，多変量解析による予後因子として，年齢，全身状態（performance status：PS），総病変数，高Ca血症，高LDH血症が同定された[13)~16)]。そして予後因子解析と臨床病態の特徴から「急性型」，「リンパ腫型」，「慢性型」，「くすぶり型」の4臨床病型分類が提唱されている[17]（表1）。これらの割合は急性型57%，リンパ腫型24%，慢性型19%，くすぶり型6%であった。急性型，リンパ腫型，予後不良因子（LDH，アルブミン，BUNのいずれか1つ以上が異常値）を持つ慢性型ATLは急速な経過をたどることがほとんどであり，それぞれの生存期間中央値（MST）は6カ月，10カ月，15カ月であることから一括してアグレッシブATLと呼ばれる。一方くすぶり型および予後不良因子を有していない慢性型ATLは比較的緩徐な経過を辿り，それぞれの4年生存割合は約63%と約70%である[18]ことから，インドレントATLと呼ばれる。

JCOG-LSGがアグレッシブATLを対象とし，継続して臨床試験を行ってきたことから，化学療法における反応性の評価では，JCOG治療効果判定規準が広く使用されてきた[14)19)]。近年では非ホジキンリンパ腫と慢性リンパ性白血病に対するもの[20)21)]をもとに改変した修正版ATLに対するJCOG治療効果判定規準[22]が用いられている（表2）。

表 1　ATL 臨床病型の診断規準（文献 17）を改変）

評価項目		くすぶり型	慢性型*1	リンパ腫型*1	急性型*1
抗 HTLV-1 抗体*2		＋	＋	＋	＋
リンパ球数（×10^3/mm^3）*3		＜4	≧4	＜4	
異常リンパ球数*4		≧5%*7	＋*8	≦1%	＋*8
Flower cell		*5	*5	no	＋
LDH		≦1.5N	≦2N		
補正 Ca 値（mg/dL）*6		＜11.0	＜11.0		
組織学的に腫瘍病変が確認されたリンパ節腫大		No		＋	
腫瘍病変	皮膚	*7			
	肺	*7			
	リンパ節	no		yes	
	肝腫大	no			
	脾腫大	no			
	中枢神経	no	no		
	骨	no	no		
	胸水	no	no		
	腹水	no	no		
	消化管	no	no		

空欄は他の病型で規定される条件以外の制約はないことを示す。
N：正常値上限
*1 予後不良因子を有する慢性型：BUN＞施設基準値上限，LDH＞施設基準値上限，血清アルブミン＜施設基準値下限の 1 つでも満たす場合
*2 PA 法あるいは ELISA 法や Western blot 法のいずれかで陽性であること。
Immunofluorescence 法や Western blot 法により，陽性反応が確認されていることが望ましい。測定可能な施設では，Southern blot 法により，HTLV-1 provirus の ATL 細胞への組み込みを確認する。
*3 正常リンパ球と異常リンパ球を含むリンパ球様細胞の実数の和
*4 形態学的に明らかな ATL 細胞
*5 ATL に特徴的な flower cell が認められてもよい。
*6 補正 Ca 値は以下の式で求める。
血清アルブミン値≧4.0(g/dL)の場合：補正カルシウム値(mg/dL)＝総カルシウム値(mg/dL)
血清アルブミン値＜4.0(g/dL)の場合：補正カルシウム値(mg/dL)＝総カルシウム値(mg/dL)－0.8［アルブミン(g/dL)－4］
*7 末梢血中の異常リンパ球が 5%未満でくすぶり型と診断されるには，皮膚あるいは肺に組織学的に腫瘍病変が確認されることが必要である。
*8 末梢血中の異常リンパ球が 5%未満で慢性型または急性型と診断されるには，組織学的に腫瘍病変が確認されることが必要である。