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Review Article

Treatment of Adult T-cell Leukemia

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Adult T-cell Leukemia (ATL) is an aggressive malignant disease of $CD4^+$ T-cells associated with human T-cell leukemia virus type I (HTLV-I). Prognosis of ATL patients is directly correlated to the subtype of ATL. Treatment of the aggressive forms (acute and lymphoma types) of ATL remains inadequate, as most ATL patients receive conventional chemotherapy without stem cell rescue. At present, LSG15 is the standard chemotherapy for the treatment of aggressive ATL, but the efficacy of LSG15 in most patients is transient. To prolong median survival time, additional therapies for maintenance of complete response (CR) are needed after achieving CR by induction chemotherapy. Improved outcome after allogeneic stem cell transplantation (allo-SCT), despite a high incidence of graft-versus-host disease, has been reported. Thus, allogeneic bone marrow transplantation and allogeneic peripheral blood SCT may have great potential for eradication of HTLV-1 and cure of ATL. Recently, reduced-intensity conditioning stem cell transplantation was also reported to be effective for ATL. Although several issues, including selection criteria for patients and sources of stem cells remain to be resolved, allo-SCT may be considered as a treatment option for patients with aggressive ATL. To evaluate whether allo-SCT is more effective than the standard chemotherapy (LSG15) for aggressive ATL, an upfront phase II clinical trial of JCOG-LSG is now being planned. Novel innovative targeted strategies, such as antiretroviral therapy, arsenic trioxide, nuclear factor-κB inhibitors, proteasome inhibitors, histone deacetylase inhibitors, several monoclonal antibodies including anti-CC chemokine receptor 4, anti-folate, purine nucleotide phosphorylase inhibitor, mTOR (mammalian target of rapamycin) inhibitor, bendamustine, small molecule Bcl-2 inhibitors and Tax-targeted immunotherapy, should be promptly studied in order to develop curative treatments for ATL in the near future. 〔*J Clin Exp Hematopathol 50(1) : 9-25, 2010*〕

Keywords: adult T-cell leukemia, conventional chemotherapy, stem cell transplantation, antiretroviral therapy, novel targeted therapy

INTRODUCTION

Adult T-cell leukemia (ATL) is an aggressive malignancy of mature peripheral T-lymphocytes closely associated with human T-cell leukemia virus type I (HTLV-1).[1,2] Thirty years have passed since ATL was first described,[3] and yet the precise mechanisms of leukemogenesis by HTLV-1 remain unclear. The clinical manifestations of ATL range from subclinical or smoldering to overt leukemia and lymphoma. ATL has been subdivided into four clinical subtypes ; acute, lymphoma, chronic and smoldering.[4] However, a fifth subtype, cutaneous type ATL was recently reported.[5,6] Prognosis of ATL patients is directly correlated with the subtype of ATL.

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In the largest published study (818 patients), the median survival time (MST) of ATL in Japan and the projected 4-year survival were 6.2 mon and 5%, respectively, for the acute type, 10.2 mon and 5.7%, respectively, for the lymphoma type, and 24.3 mon and 26.9%, respectively, for the chronic type.[4] Although therapeutic results seems to have improved over the past 20 years, MST of the standard treatment for aggressive ATL (acute and lymphoma types) remains inadequate. New definitions, prognostic factors, treatments, and response criteria for ATL were recently proposed based on international consensus under the sponsorship of the 13th International Conference on Human Retrovirology.[7] So this article reviews the current status and future potential and novel treatments of ATL.

CURRENT TREATMENT STRATEGIES

Treatment decisions should be based on ATL subtype classification[4] and prognostic factors[8,9] at onset. The prognostic factors include clinical factors, such as performance status (PS), lactate dehydrogenase (LD), age, number of involved lesions, and hypercalcemia, and several molecular

factors.

Smoldering and favorable chronic types

For asymptomatic patients, a "watch and wait (watchful waiting)" approach is recommended in the recent proposal.[7] For symptomatic patients who have skin lesions or opportunistic infections, Zidovudine (AZT)/interferon (IFN)-α or "watch and wait" is recommended. However, treatment with AZT/IFN has not yet been attempted in Japan. Thus, skin lesions are usually treated with topical corticosteroids ointments. Patients with refractory skin lesion are treated with systemic corticosteroids or orally applicable agents, such as etoposide (ETO) or sobuzoxane (MST-16). In addition, in favorable chronic type ATL, patients with leukocytosis (lymphocytosis) [white blood cell (WBC) count > 25,000 ~ 30,000] are usually treated orally with ETO or MST-16. Either ETO, 25 mg once a day (or every two days), or MST-16, 400 mg every two days, is the preferred regimen at our hospital for such cases. Dosage of these agents should be modified in order to maintain WBC count > 3,000. Interferon is apparently more effective for cutaneous lesions than for other lesions.[10,11] Psoralen plus ultraviolet A (PUVA) therapy[12] has been reported by dermatologist to be effective against generalized eruptions. Electron beam irradiation is also effective for a solitary skin nodules.[13] For cutaneous type ATL,[5,6] generalized erythema/papule and nodule/tumor are usually treated with topical corticosteroids ointment or PUVA therapy, electron beam irradiation or surgical operation or the same multiagents conventional chemotherapy as for lymphoma type ATL, respectively.

Unfavorable chronic, acute and lymphoma types

For patients with good prognostic factors, conventional chemotherapy (LSG15) or AZT/IFN should be considered as a first-line treatment, but not for patients with lymphoma type ATL.[7] Lymphoma type ATL seems to show lower and slower response with AZT/IFN treatment, thus these patients might benefit from induction conventional chemotherapy.[14] However, in Japan, these patients (all three subtypes) are usually given conventional chemotherapy (LSG15).[15,16] The treatment strategy in Japan is illustrated in Fig. 1. For elderly patients and those with poor PS LSG15 is not suitable, therefore not so intensive regimens such as RCM regimen,[17,18] OPEC/MPEC regimen[19] are preferred in our hospital. Although conventional chemotherapy is indicated for patients with unfavorable chronic type ATL, there is no evidence on whether all such patients should be treated by conventional chemotherapy.

Salvage treatment for ATL patients become refractory to prior LSG15 or relapsed after LSG15 has not been ever discussed. As a clinical practice, refractory/relapsed ATL patients are treated with the same second-line regimens as peripheral T-cell lymphomas and diffuse large B-cell lymphomas, such as EPOCH, DHAP, ESHAP, and ICE.[20]

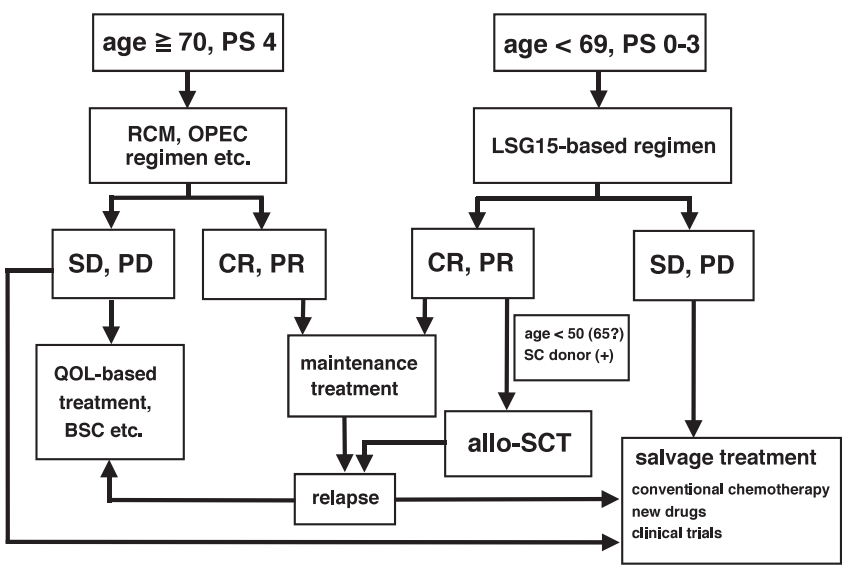

Fig. 1. Treatment strategy for acute and lymphoma type ATL in Japan. ATL, adult T-cell Leukemia ; PS, performance status ; CR, complete response ; PR, partial response ; SD, stable disease ; PD, progressive disease ; SC, stem cell ; allo-SCT, allogeneic stem cell transplantation ; BSC, best supportive care ; LSG15, RCM, OPEC, names of regimens (see text for details).

Maintenance treatment for patients with complete response (CR), partial response (PR) by induction chemotherapy also has not been ever discussed. As maintenance treatment orally applicable agents, such as ETO[19] and MST-16[21] are preferred in our hospital. Either ETO,[19,22] 25 mg every two (or three) days or MST-16,[21,23] 400 mg every two (or three) days is usually used for a long time. Dosage of these agents should be modified in order to maintain WBC count > 3,000.

For patients with poor prognostic factors, chemotherapy followed by allogeneic stem cell transplantation (allo-SCT) is recommended, while also for patients with poor response to initial therapy, allo-SCT should be considered.[7] However, in order to justify these recommendations a new prospective phase II trial to test the efficacy of allo-SCT for aggressive ATL is warranted.

OVERVIEW OF PRESENT TREATMENTS

Conventional chemotherapy

Historically, the treatment modalities for aggressive ATL have yielded relatively poor outcomes.[14,24] In the earliest therapeutic report, MST was only 4.5 mon in these patients.[25] Over the past several decades, different combination regimens of conventional chemotherapy have been reported in Japan. In particular, six prospective chemotherapeutic trials have been consecutively conducted by the Lymphoma Study Group in the Japan Clinical Oncology Group (JCOG-LSG) (Table 1). The first trial, JCOG7801 (LSG1 regimen, 1978-1980), utilized the VEPA regimen, which consisted of vincristine (VCR), cyclophosphamide (CPA), prednisolone (PSL) and doxorubicin (DOX),[26] and reported a CR rate of 18%. JCOG8101, a randomized phase III trial of LSG1-VEPA versus LSG2-VEPA-M (VEPA plus methotrexate), was conducted between 1981 and 1983.[27,28] The MST of 54 patients treated with LSG1/LSG2 was 7.5 mon, and the estimated four-year survival rate was only 8.3%. In 1987, the JCOG-LSG initiated a combination phase II study (JCOG8701 ; LSG4 regimen), combining three different regimens : (1) VEPA-B, which consisted of VCR, CPA, PSL, DOX and bleomycin (BLM) ; (2) M-FEPA, which consisted of methotrexate (MTX), vindesine (VDS), CPA, PSL and DOX ; and (3) VEPP-B, which consisted of VCR, etoposide (ETO), procarbazine (PCZ), PSL and BLM.[29] The CR rate for ATL improved from 27.8% (LSG1/LSG2) to 41.9% (LSG4). However, patients still showed poor prognosis, with an MST of eight mon and a four-year survival rate of 12%.

A phase II trial (JCOG9101 ; LSG11 regimen) was then performed using a 2'-Deoxycoformycin (DCF)-containing combination between 1991 and 1993. This regimen achieved an MST of 7.4 mon and an estimated 2-year survival rate of 15.5%,[30] which is similar to the patient outcomes seen in JCOG8701. In 1994, the JCOG-LSG initiated a new multiagent combination phase II trial (JCOG9303 ; LSG15 regimen) ; an eight-drug regimen consisting of VCAP (VCR, CPA, DOX, PSL), AMP [DOX, ranimustine (MCNU), PSL], and VECP [VDS, ETO, carboplatin (CBDCA), and PSL] in patients with previously untreated ATL.[31] Treatment may be repeated every 4 weeks for up to seven courses. LSG15 includes intra-thecal injections of MTX, cytarabin (Ara-C) and PSL during cycles 2, 4, and 6 for prophylaxis against central nervous ststem invasion[32] by ATL cells. This trial also attempted to maximize the relative dose intensity through concomitant prophylactic use of granulocyte colony-stimulating factor (G-CSF) and to reduce multi-drug resistance by incorporating non-cross-resistant agents, such as MCNU and CBDCA. Activity of MCNU and CBDCA is not affected by the expression of P-glycoprotein, a product of the *MDR1*, which is frequently expressed in ATL cells.[33] The resulting CR rate and MST was 35.5% and 13 mon, respectively, and the 2-year overall survival (OS) was 31.3%. Furthermore, this protocol was well-tolerated and yielded patients outcomes that were superior to those seen in JCOG8701 and JCOG9101.

In order to confirm whether the LSG15 is a new standard

Table 1. Clinical trials for ATL by the JCOG-LSG

trial name	period	regimen name	No. of cases	CR (%)	PR (%)	MST (months)	survival (%)
JCOG 7801	1978-1980	LSG1 (VEPA)	18	16.7	N/A	5.0	N/A
JCOG 8101	1981-1983	LSG1 (VEPA)	24	16.7	N/A	7.5	8.3 (4 yr)
		LSG2 (VEPA-M)	30	36.7	N/A		
JCOG 8701	1987-1990	LSG4	43	41.9	N/A	8.0	12 (4 yr)
JCOG 9109	1991-1993	LSG11	62	28.3	23.3	7.4	15.5 (2 yr) 10.3 (5 yr)
JCOG 9303	1994-1996	LSG15	96	35.5	45.2	13.0	31.3 (2 yr)
JCOG 9801	1998-2003	mLSG15	57	40.0	32.0	12.7	24 (3 yr)
		mLSG19	61	25.0	41.0	10.9	13 (3 yr)

JCOG, Japan Clinical Oncology Group ; LSG, Lymphoma Study Group ; m, modified ; CR, complete response ; PR, partial response ; MST, median survival time ; N/A, not available ; VEPA, vincristine, endoxan, prednisolone, adriamycin ; VEPA-M, VEPA plus methotrexate

for the treatment of aggressive subtypes of ATL, the JCOG-LSG conducted a randomized phase III study (JCOG9801) comparing the modified (m)-LSG15 with biweekly CHOP (mLSG19) (CPA, DOX, VCR, PSL), which comprises eight cycles of CHOP every two weeks.[34] In JCOG9801, the CR rate was higher for mLSG15 (VCAP-AMP-VECP) than for biweekly CHOP (40% vs 25%, respectively). OS at three years was 24% in the mLSG15 group and 13% in the biweekly CHOP group. For the mLSG15 versus mLSG19, grade 4 neutropenia, grade 4 thrombocytopenia, and grade 3 or 4 infection rates were 98% vs 83%, 74% vs 17%, and 32% vs 15%, respectively. The longer OS at 3 years and the higher CR rate with mLSG15 when compared to mLSG19 suggest that mLSG15 is a more effective regimen at the expense of higher toxicity.

Based on the above clinical studies, at present, the gold standard chemotherapy for aggressive ATL (i.e., acute, lymphoma, or unfavorable chronic type ATL) in patients aged 15-69 years appears to be the LSG15-based regimen (mLSG15 regimen).

Another clinical trial in Japan using the CHOP-V-MMV regimen consisting of VCR, VDS, DOX, mitoxantrone (MIT), CPA, ETO, MCNU, and PLS with prophylactic support by G-CSF have been reported.[35] That study showed a mild improvement in the response rate (CR 34.6%, PR 39.5%) and MST was 8.5 mon with a predicted 3-year survival of 13.5%. These results and those of LSG15 indicate that the dose-intensity of these protocols is unable to produce a cure in patients with ATL.

RCM (response-oriented cyclic multidrug) protocol, which aimed to increase the dose intensity of chemotherapy, to individualize treatments based on the patient response, and to avoid multi-drug resistence[33,36,37] of ATL cells, by weekly exchange of non-cross-resistant drugs (CPA, VDS, MCNU, PSL, MTX, Pirarubicin, ETO, Peplomycin, Ara-C, Mitomycin-C, and DOX), resulted in a CR rate 20.9%, a PR rate of 65.1%, and an MST of 6.0 mon.[17] These chemotherapeutic results are equal or superior to outcomes seen in other trials, despite the high proportion of patients with a poor PS (PS 3 or 4). Thus, response-oriented chemotherapy appears to be the most efficacious of all presently available therapy for ATL patients with poor prognostic factors. Although addition of G-CSF to the RCM protocol improved CR (64.7 %) and PR (23.5%), it had no effect on MST (7.4 mon).[18] Moreover, the clinical characteristics of elderly patients with ATL, immunosuppression, hypercalcemia, multi-organ failure (particularly kidney and liver dysfunction), and poor PS prevent the administration of intensive treatment. However, long-term maintenance chemotherapy with OPEC/ MPEC (VCR or MTX, PSL, ETO, CPA) or with daily oral ETO and PSL (DOEP) may improve quality of life (QOL) in ATL patients.[19] Thus, the RCM protocol and OPEC/MPEC and DOEP regimen are suitable for use in ATL patients with poor prognostic factors.

The disappointing results with conventional chemotherapies for patients with ATL have led to a search for new active chemotherapeutic agents. For example, Ohno *et al*. treated 23 ATL patients with MST-16, a bis (2, 6-dioxopiperazine) analogue that inhibits topoisomerase II, and reported a response rate of 43.5% (two patients with CR and eight patients with PR).[38] Tsuda *et al*. treated 13 ATL patients with irinotecan hydrochloride (CPT-11), a semi-synthetic analogue of campothecin that inhibits the topoisomerase I, and reported a response rate of 38.5% (one patient with CR and four patients with PR) without any major toxicity.[39] Despite these promising results, to our knowledge, no multi-institutional large-scale combination chemotherapy trial including these new agents has been performed. Consequently multi-institutional large-scale clinical trials are required before these agents can be widely applied.

With regard to clinical characteristics, most ATL patients undergo conventional chemotherapy without stem cell rescue. Currently, LSG15 is the standard chemotherapy regimen for the treatment of aggressive ATL. However, the effects of LSG15 in most patients are usually transient. Thus, other therapies are required for the maintenance of CR after the LSG15 regimen. In Japan, long-term low-dose therapy with orally applicable agents such as ETO or MST-16 is frequently used for maintenance treatment after induction regimens to improve the OS of ATL patients. These orally applicable agents may be useful for palliative therapy in elderly patients or those with poor PS.

In daily practice, patients with acute and lymphoma type ATL are treated in our institution using the strategy illustrated in Fig. 1. The LSG15-based regimen is the first choice for ATL patients with an indication of intensive multi-drug chemotherapy. There are no standard treatments with an evidence for benefit for elderly patients or those with poor PS. These patients are therefore treated by regimens that aim to maintain a QOL, such as the RCM protocol,[17,18] and the OPEC/MPEC regimen.[19] ATL patients obtaining CR or PR by these induction treatments are treated with maintenance regimens, such as long-term low-dose therapy by using orally applicable agents ETO or MST-16. Either ETO, 25 mg once a day (or every two days), or MST-16, 400 mg every two days, is the preferred regimen in our hospital. These agents may be useful as palliative therapy (QOL-based treatment) for elderly patients or those with poor PS, but prospective clinical trials of these long-term low-dose therapies remain necessary. Effective second line conventional chemotherapy for relapsed or refractory ATL patients has not yet been reported. Relapsed or refractory ATL patients have been treated with regimens according to the guidelines for non-Hodgkin lymphoma (NHL). Suitable salvage treatments for ATL patients therefore need to be devised.

Stem cell transplantation

As LSG15 is insufficient to achieve a cure in patients with ATL, bone marrow transplantation (BMT) has been attempted. High-dose chemotherapy with autologous BMT or with autologous peripheral blood stem cell transplantation (PBSCT) has been reported in only nine patients,[40,41] all of whom relapsed or died from transplant-related mortality. However, early reports of allogeneic BMT (allo-BMT) described the successful treatment of several patients with ATL in the late 1990s[42,43] despite a high incidence of toxic effects and transplant-related death.[44,45] Since then, other studies have described improved outcome after allo-BMT, despite a high incidence of graft-versus-host disease (GVHD).[46,47] For example, Utsunomiya *et al*. studied 10 patients with ATL treated with allo-BMT and reported a MST 17.5 mon.[46] Six of these ten patients developed acute GVHD, and two patients with no GVHD relapsed with clinical ATL.

In another study,[47] four of 11 patients were alive and disease-free at a median follow up of 25 mon, and 5 of these eleven patients developed acute GVHD. Graft-versus-adult T-cell leukemia (Gv-ATL) after allo-SCT may have also contributed to the eradication of ATL cells.[48] Moreover, HTLV-1 proviral DNA loads were reduced to undetectable levels in peripheral blood mononuclear cells sampled 12 mon after BMT[49] and 10 mon after non-myeloablative allogeneic PBSCT.[50] A retrospective study of 40 patients of allo-SCT in seven institutions in Japan between 1997 and 2002 confirmed remarkable improvements in MST and in 3-year OS (9.6 mon and 45.3%, respectively).[51] Most ATL patients lack a suitable HLA-matched related donor and require an HTLV-1-negative unrelated donor, and yet there has been little information regarding the outcome of unrelated BMT for ATL. The feasibility of allo-SCT from unrelated donors has recently been reported.[52,53] Taken together, allo-BMT and allo-PBSCT have great potential for eradication of HTLV-1 and cure of ATL.

Recent reports have suggested that reduced-intensity conditioning stem cell transplantation (RIST) may also be effective for the treatment of ATL.[54-57] Large-scale multi-center phase II clinical trials are reported to evaluate whether allo-BMT or non-myeloablative allo-PBSCT are effective for ATL.[55] Umbilical cord blood from unrelated donors has been used as an alternative stem cell source for adult patients with hematological malignancies, including ATL.[58,59] In one successful case of ATL with unrelated cord blood transplantation (UCBT), the patient remained in complete remission at 30 mon after UCBT and her HTLV-1 proviral load remained at undetectable levels.[60] Although the therapeutic effectiveness of UCBT for ATL needs to be determined in future clinical trials, UCBT may be a potential option for ATL patients without suitable donors and who urgently require treatment. Moreover, allo-SCT for refractory ATL using HLA-incompatible related donor stem cells has been reported.[61,62] HLA-matched related donors are available for only a limited number of patients, so allo-SCT from HLA-haploidentical donors could be another option of stem cell sources.

Although selection criteria with respect to previous treatment, stem cell source, and HTLV-1 viral status of the donor remain to be determined, allo-SCT may be considered as a treatment option for patients with aggressive ATL.[63] To evaluate whether allo-SCT is more effective than the standard conventional chemotherapy (LSG15) for aggressive ATL, a new upfront phase II clinical trial of JCOG-LSG is now being planned. However, until allo-SCT is shown to be superior as an induction treatment for LSG15 in a new clinical trial, it is not the best evidence-based modality for the treatment of ATL (Fig. 1).

Supportive therapy

Infectious complications are one of the major causes of death in patients with ATL. Particularly pneumocystis pneumonitis (PCP) and cytomegalovirus (CMV) infections are frequently encountered among patients with ATL. At initial presentation, 26.0% of patients with ATL have infectious complications, more than half of which were fungal, *Pneumocystis jirovecii*, and viral infection.[4] Therefore patients with ATL require some supportive or preventive therapies for fungal, *Pneumocystis jirovecii*, and viral infections. A low dose Trimethoprim-Sulfamethoxazole and oral antifungal agents, such as fluconazole, and itraconazole are now recommended for prophylactic use together with chemotherapeutic drugs.

FUTURE PERSPECTIVES ON NOVEL TREATMENTS

As conventional chemotherapy and SCT cannot achieve cure in ATL patients, new therapies are required to specifically target leukemic cells, HTLV-1, Tax protein, nuclear factor (NF)-κB, proteasome, histone deacetylase (HDAC), and the secondary genetic events of leukemogenesis. Following drugs are under investigation for the treatment of patients with ATL.

New chemical anti-tumor agents

1) Antiretroviral therapy

Several phase II trials have been conducted.[64-69] Gill *et al*. in the United States reported that treatment with AZT/IFN produced an objective response in 11 (five CR, six PR) of 19 patients with acute or lymphoma type ATL,[64] while a French group reported that the regimen produced an objective response in all five ATL patients that they treated.[65] Although the results with AZT/IFN are encouraging, the overall surviv-

al of previously untreated ATL patients was rather short (4.8 mon)[66] when compared to those on the LSG15 regimen.[31] Furthermore, the CR rate with AZT/IFN in previously untreated ATL patients, 25% (3/12), was not superior to the CR rate in those treated with LSG15. On long-term follow up of 15 ATL patients treated over a 4-year period, AZT/IFN improved outcome (MST of 18 mon),[67] possibly due to maintenance treatment with AZT/IFN after achieving a PR.

More recently, a prospective phase II clinical trial reported that the use of AZT/IFN as an initial treatment in 19 ATL patients (15 acute type and four lymphoma type),[68] resulted in a 92% response rate (RR; 58% CR and 33% PR) and a MST of 11 mon for all patients. While this MST is still shorter than that achieved by treatment with LSG15, these studies confirm the efficacy and safety of AZT/IFN in patients with ATL. In these studies, high doses (6 to 9 million units of IFN-α and daily divided AZT doses of 800 to 1,000 mg) of both agents are recommended. Although no randomized trials have yet been performed, these results are very encouraging, and it appears that a combination of new antiretroviral drugs improves the long-term outlook for patients with ATL.

A worldwide meta-analysis on the use of AZT/IFN for ATL in 209 patients treated from 1994 to 2006 was recently presented at the 13th International Conference on Human Retrovirology and at the 49th Annual Meeting of the American Society of Hematology.[7] In 100 patients receiving first-line AZT/IFN therapy, a RR was 66%, with 43% of patients achieving CR, MST was 24 mon, and the 5-year OS rate was 50%. In 84 patients receiving first-line chemotherapy, these values were 7 mon and 20%, respectively. The MST values for patients with acute type ATL treated with first-line AZT/IFN and chemotherapy were 12 and 9 mon, respectively. The values for patients with lymphoma type ATL were 12 and 15 mon, respectively. Thus, patients with lymphoma type ATL did not benefit from AZT/IFN therapy, while patients with chronic and smoldering type ATL treated with first-line AZT/ IFN therapy showed 100% OS at a median follow-up time of 5 years. These results suggest that treatment of ATL by AZT/IFN therapy caused high response and CR rates, particularly in acute, chronic and smoldering types ATL. This retrospective analysis showed the promising results, therefore, further studies comparing AZT/IFN and conventional chemotherapy in acute type ATL are warranted. Particularly in Japan, where treatment with AZT/IFN has not yet been attempted, clinical trials of AZT/IFN therapy are thus needed immediately.

The mechanism of action of AZT/IFN remains unclear, but may involve antiviral effects mediated by inhibition of HTLV-1 replication rather than via direct antiproliferative effects on leukemic cells.[70] For example, in patients with HTLV-1-associated myelopathy (HAM), reduction of HTLV-1 viral DNA load was reported during treatment with the reverse transcriptase inhibitor lamivudine,[71] and HTLV-1 replication was inhibited by the nucleoside reverse-transcriptase inhibitors tenofovir, abacavir, lamivudine, zalcitabine, stavudine, zidovudine and didanosine.[72,73] Another report described the successful treatment of a patient with ATL using zidovudine, lamivudine and IFN-α.[74] Thus, antiretroviral treatment appears to be a promising strategy for the treatment of ATL as a viral infectious disease, but further studies are required in order to elucidate the mechanisms of the anti-ATL effects.

2) Arsenic trioxide

Arsenic trioxide, very effective against acute promyelocytic leukemia (APL), inhibits the growth of HTLV-1 infected T-cell lines and fresh ATL cells via induction of apoptosis.[75] Furthermore, arsenic trioxide and IFN-α act synergistically to induce cell cycle arrest and apoptosis in HTLV-1- infected T-cells.[76] It has been demonstrated that apoptosis by arsenic trioxide in HTLV-1-infected T-cell lines was induced via activation of caspase pathway.[77,78] Sodium arsenite ($NaAsO_2$) was shown to induce apoptosis by down-regulating survivin expression through the NF-κB pathway in ATL cell lines.[79]

Therapeutic results of phase II trials for arsenic trioxide and IFN-α have been conducted in seven patients (four acute type, three lymphoma type) with relapsed/refractory ATL,[80] and although four patients showed an initial response (one CR and three PR), treatment was discontinued after a median of 22 days because of toxicity (three patients) or subsequent progression (four patients). The combination of arsenic trioxide and IFN-α is feasible and exhibits anti-leukemic effects in relapsed/ refractory ATL patients. Recently, Ishitsuka *et al*. reported the therapeutic effectiveness of arsenic trioxide with or without IFN-α in patients with relapsed/refractory ATL.[81] Two patients given a combination of arsenic trioxide and IFN-α showed PR. More recently, in a prospective phase II study of arsenic trioxide, IFN-α, and AZT for 10 patients newly diagnosed with chronic type ATL,[82] an impressive 100% RR was observed, including 7 CR and 3 PR with moderate and manageable hematologic toxicity.

Cancer-initiating cells (CICs) and leukemia-initiating cells (LICs) remain unaffected by both conventional chemotherapy and targeted therapy.[83] Hence, leukemia relapse can occur after a period of latency, as quiescent LICs that can reinitiate leukemia are not eradicated. Therefore, development of new therapeutic approaches targeting LICs may have a profound impact on leukemia eradication. Arsenic trioxide has recently been shown to eradicate quiescent LICs.[84,85] In particular, arsenic trioxide followed by Ara-C seems to significantly increase the efficacy of Ara-C-mediated induction of apoptosis resulting in eradication of LICs.[85] Because cancer stem cells (CSCs) in ATL have recently been identified,[86] single use of arsenic trioxide or arsenic trioxide in combination with chemotherapeutic drugs for the treatment of ATL needs to be

reexamined.

Irrespective, further studies are sorely required in order to assess the optimal timing and combination of arsenic trioxide.

3) Retinoid derivatives

All-trans retinoic acid (ATRA) is used in combination chemotherapy for standard induction therapy in patients with APL. However, retinoids also affect fresh ATL cells and ATL cell lines.[87-89] For example, 13-cis retinoic acid (13-cis RA) and ATRA inhibits growth of ATL cell and ATL cell lines, and causes apoptosis, possibly by blocking the Tax/NF-κB signaling pathway[90] or by down-regulating Bcl-xl.[91] Furthermore, the synthetic retinoid N-(4-hydroxyphenyl) retinamide also induces growth arrest and apoptosis in HTLV-1-transformed cells.[92] Indeed, ATRA may be useful treatment for patients with chemotherapy resistant acute type ATL,[93] and ATRA and arsenic trioxide produce synergistic effect when used from the treatment for ATL patients.[94] Treatment results for 20 patients with ATL were recently reported.[95] The efficacy of ATRA was as follows : 2 PR, 2 no change (NC), 3 progressive disease (PD) in 7 acute type ATL, 3 PR in 3 lymphoma type ATL, 1 PR, 3 NC in 4 chronic type ATL, and 2 PR, 4 NC in 6 smoldering type ATL. These data suggest that retinoids are effective, but have limited efficacy. However further study is needed in order to elucidate whether combination use with arsenic trioxide is effective. Novel synthetic retinoid derivatives, such as NIK-333[96] and Am80 (Tamibarotene),[97] are potentially useful therapeutic agents against ATL.

4) NF-κB inhibitors

Activation of the NF-κB pathway, either through Tax-dependent or Tax-independent mechanisms, has been reported to play a crucial role in the proliferation of leukemia cells, protection from apoptosis, and drug resistance in ATL.[98-101] An inhibitor of NF-κB, Bay 11-7082, was found to induce apoptosis of HTLV-1-infected T-cell lines and primary ATL cells,[102] and to prevent primary tumor growth and leukemic infiltration in various organs in an *in vivo* mouse model of ATL.[103] Another inhibitor of NF-κB, dehydroxymethylepoxyquinomycin (DHMEQ ; a 5-hydroxymethyl derivative of epoxyquinomicin C) inhibits NF-κB activation in primary ATL cells and cell lines derived from patients with ATL, thereby inducing apoptotic cell death.[104] DHMEQ induces apoptosis in HTLV-1-transformed cells in a mouse model of ATL.[105] Recently, fucoxanthin, fucoxanthinol and indole-3-carbinol have been reported to inactivate NF-κB and be potentially useful therapeutic agents for patients with ATL.[106,107] However, further clinical studies regarding the activity of NF-κB inhibitors on patients with ATL is required for full characterization of their clinical utility.

5) Proteasome inhibitors

Bortezomib (PS-341), a peptidyl boronic acid inhibitor of the proteasome, shows potent action against a wide range of hematologic malignancies and has been shown to inhibit NF-κB. A phase II trial in certain subtypes of NHL has demonstrated that bortezomib is well tolerated and exerts significant activity when used as a singe agent.[108] Bortezomib also inhibits the degradation of I-kBα (NF of κ light polypeptide gene enhancer in B-cells inhibitor-α) in ATL cells, resulting in suppression of NF-κB and induction of cell death in ATL cells *in vitro*.[109] When bortezomib was administered into SCID mice bearing tumors derived from ATL cells, it suppressed tumor growth *in vivo*. These results indicate that bortezomib is effective against ATL cells *in vitro* and *in vivo* by inducing apoptosis.[109] Moreover, it has been reported that Bortezomib affects multiple pathways critical for the survival of HTLV-1-infected T-cells, supporting a potential therapeutic role for bortezomib in ATL.[110] One patient with ATL in a clinical trial did not respond to bortezomib.[111] Recently, Bortezomib was reported to exhibit synergistic anti-tumor effects with histone deacetylase inhibitor for ATL cells *in vitro* and *in vivo*.[112] To evaluate the clinical efficacy of bortezomib in patients with ATL, large-scale phase II trials of bortezomib with or without other chemotherapeutic agents are urgently required.

6) Histone deacetylase (HDAC) inhibitors

Inhibition of HDAC activity promotes growth arrest, differentiation and apoptosis in a variety of transformed cells *in vitro* and *in vivo*, including malignancies originating from lymphoid cells.[113,114] In contrast, HDAC inhibitors are relatively nontoxic when compared to normal cells.[113] FR901228 (depsipeptide, FK228, romidepsin), isolated from *Chromobacterium violaceum*, is a member of the cyclic peptide class of HDAC inhibitors and is currently in use in clinical trials to determine its anticancer efficacy.[115] The results using FR901228 in patients with cutaneous T-cell lymphoma (CTCL) suggest significant activity in that disease.[114] Furthermore, FR901228 can induce apoptosis in HTLV-1-infected T-cell lines and primary ATL cells.[116]

Romidepsin was recently reported to have single-agent clinical activity with significant and durable responses in patients with CTCL.[117] Efficacy with an acceptable safety profile of vorinostat (suberoylanilide hydroxamic acid, SAHA) for patients with refractory CTCL was confirmed in a multicenter clinical trial.[118] Several HDAC inhibitors [Vorinostat (SAHA), panobinostat (LBH589), and MS-275] effectively inhibited the proliferation of HTLV-1-infected T-cell lines and freshly isolated ATL cells.[119] Novel non-hydroxamate HDAC inhibitor, NCH-51 exhibited cytotoxicity for the lymphoid malignant cells at higher levels than SAHA.[120] Taken together, HDAC inhibitors thus appear to be promising novel agents for ATL and should soon be examined for their therapeutic utility in patients with ATL by clinical trials.

7) Anti-folate, purine nucleotide phosphorylase inhibitor

Pralatrexate, a 10-deazaaminopterin, is a novel inhibitor of dihydrofolate reductase. An early phase study of pralatrex-

ate has demonstrated dramatic activity in patients with relapsed/refractory lymphoma.[121] All four patients with T-cell lymphoma including one ATL patient of 20 lymphoma patients in this study achieved a CR. In other study, 14 (54%) of 26 patients with T-cell lymphoma showed CR (8 patients) and PR (6 patients).[122] Skin erosions has been reported to be *in vivo* evidence of pralatrexate-induced tumor cell apoptosis in the epidermis of a patient with ATL.[123] Further clinical trials are needed for the information on the efficacy of pralatrexate for ATL.

Forodesine (BCX-1777), a potent inhibitor of purine nucleoside phosphorylase (PNP), is highly active in primary leukemia cells in patients with chronic lymphocytic leukemia (CLL).[124,125] Although objective responses were not observed in the clinical study of forodesine for refractory T-cell malignancies,[126] large-scale phase II clinical trials of this promising antileukemic agent are clearly warranted. In Japan phase I study of forodesine for T/NK malignancies is now in progress.

8) Other agents at clinical stage

Lenalidomide (Revlimid) is a novel immunomodulatory agent with antiproliferative activities. Recent phase II study demonstrates that oral lenalidomide produces durable responses in patients with relapsed or refractory indolent NHL with a manageable tolerability profile.[127] Based on durability, further investigation of lenalidomide as maintenance therapy or in combination with other agents is warranted particularly in patients with indolent ATL.

Everolimus is the second-generation mTOR (the mammalian target of rapamycin) inhibitor, and is safe and relatively well-tolerated, potentially attractive as single agents for hematological malignancies. Several clinical trials using everolimus for refractory or advanced NHL are on going in Japan, Europe and USA.[128] Everolimus might be promising for the treatment of patients with ATL.

Bendamustine is a novel agent consisting of a mechlorethamine group, a benzimidazole ring and a butyric butyric acid side chain. Bendamustine plus rituximab is an active combination in patients with relapsed indolent lymphoma.[129] Bendamustine might have a potential therapeutic activity for patients with ATL.

Small molecule Bcl-2 inhibitors, such as oblimersen sodium (Bcl-2 antisense oligonucleotide),[130] obatoclax (GX15-070),[131] gossypol (its λ-isomer, AT-101),[132,133] and ABT-737 (its orally active analogue, ABT-263)[134] have shown to induce apoptosis in CLL cells.[135] Because clinical trials of these drugs targeting the bcl-2 family are on going, further evaluation of its activity for ATL patients is sorely required.

Denileukin diftitox (Ontak) is a fusion protein (not a monoclonal antibody) that consists of the full-length sequence of the interleukin-2 (IL-2) protein genetically fused to the enzymatically active and translocating domains of diphtheria toxin. Relapsed/refractory ATL with resistance to previous AZT/IFN and arsenic trioxide/IFN treatment was reported to have a CR with monotherapy of denileukin diftitox.[136] Further clinical studies examining efficacy of denileukin difitoxon for patients with relapsed/refractory ATL is warranted.

9) Other agents at pre-clinical stage

Pyrrolidine dithiocarbamate (PDTC) was originally known as an anti-oxidant.[137] PDTC selectively inhibits HTLV-1 Tax protein-induced activation of NF-κB and induces apoptosis in colorectal cancer cells.[138] We demonstrated that PDTC induce apoptosis in ATL cells and HTLV-1- infected T-cell lines and that HTLV-1 Tax protein inhibits PDTC-induced apoptosis.[139]

EAPB0203, a member of the imidazoquinoxaline family, inhibits growth and induces caspase-dependent apoptosis in T-cell lymphoma and ATL.[140] EAPB0203 may play a potential therapeutic role in ATL either as a systemic or topical treatment for lymphomatous skin lesions.[140]

Nutlin-3a, an antagonist of MDM2, induces apoptosis and cellular senescence in ATL cells. The combinatory use of TRAIL (tumor necrosis factor-related apoptosis-inducing ligand)-related drugs may be one of the most rational choices for Nutlin-3a based treatments.[141]

Deguelin, naturally occurring rotenoid, showed a potent anti-proliferative effect on HTLV-1- transformed T-cells.[142]

Curcumin, the major yellow pigment in turmeric, targeted Akt cell survival signaling pathway in HTLV-1-infected T-cell lines.[143] Akt targeting agents could be useful for the treatment of ATL.

Although these agents are potentially promising compounds for the treatment of ATL, anti-proliferative effects are all demonstrated only by *in vitro* studies. So, further clinical investigations are sorely needed.

Monoclonal antibodies

Monoclonal antibodies (mAbs) are a very attractive approach in the treatment of ATL because of the decreased adverse effect in comparison with conventional chemotherapy. Use of unlabelled or radiolabelled mAbs that target the several surface antigens of ATL cells have showed promising results.

1) Anti-CC chemokine receptor 4 (CCR4)

ATL cells frequently express a chemokine receptor, CCR4, which is expressed on T helper type 2[144] and regulatory T (Treg) cells.[145] A defucosylated chimeric anti-CCR4 mAb, KM2760, induced CCR4-specific antibody-dependent cellular cytotoxicity (ADCC) against CCR4-positive ATL cell lines and primary leukemia cells obtained from ATL patients.[146,147] In addition defucosylated anti-CCR4 mAb showed potent ADCC-mediated anti-tumor effect in the ATL model mouse.[148,149] More recently phase I study of KW-0761, a next generation humanized anti-CCR4 mAb, with a defucosylated Fc region, which markedly enhanced ADCC

due to increased binding affinity to the Fcγ receptor on effector cells, has been reported in patients with relapsed CCR4-positive ATL and other peripheral T-cell lymphomas (PTCL).[150] In 15 patients only one patient, at the 1.0 mg/kg dose, developed grade 3 dose-limiting toxicities, skin rash and febrile neutropenia, and grade 4 neutropenia. Five patients (31%) achieved objective responses (2CR + 3PR). KW-0761 was tolerated at all the dose levels tested, and demonstrating potential efficacy against relapsed CCR4-positive ATL and PTCL. Therefore further clinical investigation including a single agent large-scale phase II and combination studies with conventional chemotherapeutic agents are awaited in patients with ATL and PTCL.

2) Anti-CD25

The observation that most ATL cells express CD25 (α-chain of IL-2 receptor) has prompted clinical trials of mAb to CD25 for patients with ATL.[151,152] One trial demonstrated that anti-CD25 antibody produced an objective response in six (32%) of 19 patients (two CR, four PR) that lasted from nine weeks to more than three years. However, one of the significant impediments to this approach is that leukemia cells shed a significant quantity of soluble IL-2 receptor (R) into the blood. Other strategies using anti-CD25 are conjugation with an immunotoxin (*Pseudomonas* exotoxin) or radioisotope (Yttrium-90-labelled).[153-155] Improved therapeutic efficacy of combination treatment using animal model with anti-CD25 and flavopiridol, an inhibitor of cyclin dependent kinases,[156] and PS-341 (Bortezomib)[157] were also reported. A paradigm has emerged that the combination of a monoclonal antibody with chemotherapeutic reagents that function via different mechanisms of action may be greater than additive in their cytotoxic action. The combination of daclizumab (Zenapax), a mAb targeted at the IL-2R-α (CD25), and depsipeptide (FR901228, FK228) has enhanced the antitumor effect in the treatment of a murine model of ATL.[158] These promising results may support clinical trials of anti-CD25 antibodies in the treatment of patients with ATL.

3) Anti-CD2, anti-CD52, anti-transferrin receptor (CD71), and anti-CD30

MAbs against CD2 (MEDI-507) and CD52 (Campath-1H) have shown therapeutic efficacy for a murine model of ATL.[159,160] Further, use of humanized anti-CD52 (Alemtuzumab) has produced an overall response rate of 76% (60% CR) in 39 patients with T-cell prolymphocytic leukemia and 100% in 3 patients with CTCL.[161] However, ATL patient is limited to only single case. Moreover, in recent report of phase II study of alemtuzumab in combination with pentostatin, one patient with ATL achieved a CR.[162] So, further large-scale clinical studies are required to clarify the efficacy of anti-CD52 in the treatment of patients with ATL.

A neutralizing mouse mAb (A24) directed against the transferrin receptor has been also effective in inducing apoptosis of ATL cells.[163] In addition, A24 has a synergistic effect with chemotherapy to eradicate ATL cells.[164] A24 seems to be a new attractive treatment for patients with ATL.

More recently SGN-30, a chimeric anti-CD30 mAb, and SGN-35, a monomethyl auristatin E-conjugated anti-CD30 mAb have reported to show growth-inhibitory activity against the HTLV-1-infected cell lines by apoptosis and/or cell growth arrest *in vitro*. Both mAbs significantly inhibited the growth of HTLV-1-infected cell tumors in the ATL model mice.[165]

4) Anti-angiogenic therapy

Increased microvessel density in involved organs such as skin and bone marrow in ATL patients has been reported.[166] Treatment with IFN/AZT reduced plasma levels of vascular endothelial growth factor (VEGF).[167] Although the efficacy of bevacizumab, an anti-VEGF mAb, in the treatment of NHL, is under evaluation,[168] anti-angiogenic therapy of ATL might be potentially interesting.

Overall, several mAbs may be useful in the therapy of ATL, however further clinical trials are needed to define their roles in the treatment strategy of ATL.

Vaccination

HTLV-I specific cytotoxic T-lymphocytes (CTLs) can be induced in *in vitro* cultures of peripheral blood mononuclear cells (PBMC) from HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients and asymptomatic HTLV-1 carriers, but rarely from ATL patients[169,170] Among HTLV-1 antigens, Tax is a main target for HTLV-1 specific CTLs found in HTLV-1 infected patients. HTLV-1 Tax-specific CTLs are capable of lysing short-term cultured ATL cells *in vitro*.[171] HTLV-1 Tax-specific CTLs might contribute to antitumor effects in HTLV-1 infected patients. In rat models, the antitumor effects was mediated by T-cells directed to HTLV-1 Tax.[172] Furthermore, Tax-directed vaccination eradicated ATL-like lymphomas.[173] In ATL patient, CR following non-myeloablative allogeneic PBSCT from HLA-identical sibling donors, the frequency of Tax11-19-specific $CD8^+$ CTLs markedly increased after PBSCT.[57] A strong graft-versus-HTLV-1 response occurred in the post-PBSCT ATL patient. Similar reactivation of Tax-specific CTLs was also observed in other post-PBSCT ATL patients who obtained CR. These CTLs might participate in the maintenance of CR in patients with ATL.[174] Tax-targeted immunotherapy might be worth in ATL patients. Indeed, successful generation of CTLs responses against human epitopes from Tax protein has been demonstrated in mouse model using multivalent peptide vaccination strategies against HTLV-1.[175,176] Reactivation of Tax-specific CTLs by vaccines (peptide, DNA, and viral vectors) may be promising for prophylaxis of ATL in the high-risk group of HTLV-1 carriers and for therapy of ATL in patients whose tumor cells are capable of expressing Tax.[177] A small-scale clinical trial of immunother-

apy in ATL patients is awaited in the near future.

Prevention

The prevention of HTLV-1 infection has been established in some HTLV-1 endemic areas in Japan by screening for HTLV-1 among blood donors and refraining from breast feeding among women with HTLV-1 carrier. However, the prevention of ATL development among HTLV-1 carriers has not been established because the predictive factors of disease development remain unknown. Therefore, a cohort study of HTLV-1 carriers (JSPFAD : Joint Study of Predisposing Factors for ATL Development) is ongoing nationwide in Japan. Anti-retroviral therapy for healthy HTLV-1 carriers or vaccination against HTLV-1 should be exploited as the best preventive measure.

CONCLUSION

The current standard treatment for aggressive ATL remains inadequate. However, conventional chemotherapy should be the first-line option of treatment for most of ATL patients at present. Allo-SCT by use of conventional or non-myeloablative conditioning should be considered in young patients as the clinical trials. Although maintenance treatments after CR+PR have not been investigated, for the prolongation of MST, further maintenance treatments might be needed. Moreover, therapeutic approach combining initial multidrug chemotherapy with antiretroviral therapy is an interesting option. New innovative targeted strategies including antiretroviral therapy, NF-κB inhibitors, proteasome inhibitors, HDAC inhibitor, mAbs and Tax-targeted immunotherapy could cause a cure to patients with ATL.

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