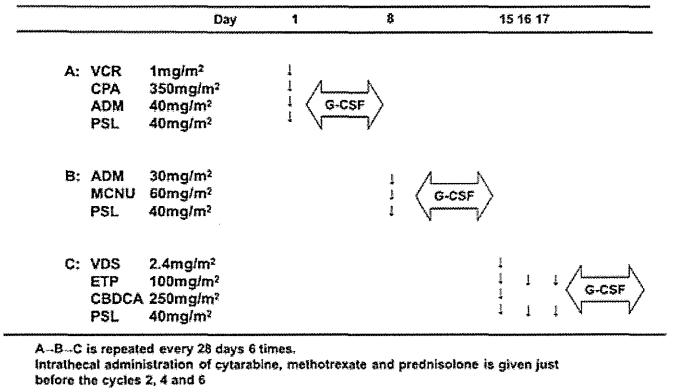

Fig. 1. Regimen of VCAP-AMP-VECP in mLSG15. VCAP = vincristine (VCR), cyclophosphamide (CPA), doxorubicin (ADM), prednisone (PSL); AMP = ADM, ranimustine (MCNU), PSL; VECP = vindesine (VDS), etoposide (ETP), carboplatin (CBDCA) and PSL. * MCNU and VDS are nitrosourea and vinca alkaloid, respectively, 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.

CHOP-14 may be explained by the more prolonged, dose dense schedule of therapy in addition to 4 more drugs. In addition, agents such as carboplatin and ranimustine not affected by multidrug-resistance (MDR)-related genes, which were frequently expressed in ATL cells at onset, were incorporated [10]. However, the MST of 13 months in VCAP-AMP-VECP (mLSG15) still compares unfavorably to other hematological malignancies, requiring further effort to improve the outcome.

Interferon-alpha and zidovudine

In 1995, Gill and associates reported that 11 of 19 patients with acute- or lymphoma-type ATL showed major responses (5 CR and 6 PR) to a combination of IFN and zidovudine (AZT) [41]. The efficacy of this combination was also observed by Hermine and associates; major objective responses were obtained in all five patients with ATL (four with acute type and one with smoldering type) [42]. 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) [43]. Since then, several small phase II studies using AZT and IFN have shown responses in ATL patients. The therapeutic effect of AZT and IFN is not a direct cytotoxic effect of these drugs on the leukemic cells. Enduring AZT treatment of ATL cell lines resulted in the inhibition of a telomerase, reprograming the cells to a p53-dependent senescence [44].

Recently, the results of a "meta-analysis" on the use of IFN and AZT for ATL were reported [45]. 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 MST 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 MST 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. However, because of the retrospective nature of this meta-analysis based on medical records at each hospital, the decision process to select the therapeutic modality for each patient and the possibility of interference with OS by second-line treatment remains unknown. 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.

Researchers from the UK reported the results of a retrospective analysis in 73 patients with aggressive ATL (acute ATL, 29; lymphoma ATL, 44) and suggested that chemotherapy with concurrent/

sequential IFN/AZT as initial treatment might improve survival for both the acute- and lymphoma-types of ATL compared with chemotherapy alone [46].

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 [47]. 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 toxicities and should be evaluated with caution.

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT)

Hishizawa and coworkers reported the results of a nationwide retrospective study in 386 patients with ATL who underwent allo-HSCT between 1996 and 2005 with several kinds of conditioning regimens [48]. The 3-year OS for the entire cohort was 33% (95% CI, 28%–38%). Multivariable analysis revealed 4 recipient factors for a poor prognosis: older age (>50 years), male sex, status other than CR, and use of unrelated cord blood compared with use of HLA-matched related grafts. Treatment-related mortality was higher among patients given cord blood transplants; disease-associated mortality was higher among male recipients or those given transplants not in remission. Among patients who received related transplants, donor HTLV-1 seropositivity adversely affected disease-associated mortality. Using the same cohort, it was recently found that the development of mild-to-moderate acute GVHD confers a lower risk of disease progression and a beneficial influence on survival among allografted patients with ATL [49].

In addition to conventional allo-HSCT, Okamura and associates reported the results of consecutive multicenter feasibility studies of reduced-intensity allo-HSCT against ATL [50]. Analysis of the combined data from both studies disclosed that grade I-II acute GVHD was the only factor that favorably affected OS and PFS and the long term prognosis after RIST was promising [51].

More recently, an expanded cohort of the above studies was analyzed for a comparison of myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) for allo-HSCT [52]. Although no significant difference in OS between MAC and RIC was observed, there was a trend indicating that RIC contributed to a better OS in older patients. Regarding mortality, RIC was significantly associated with ATL-related mortality compared to MAC.

The minimal residual disease after allo-HSCT detected as HTLV-1 proviral load was much less 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 [47].

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. Recently, a patient in whom ATL derived from donor cells developed four months after transplantation of stem cells from a sibling with HTLV-I was reported [53]. To evaluate the efficacy of allo-HSCT more accurately, especially in view of a comparison with intensive chemotherapy alone, a prospective multicenter phase II study of mLSG15 chemotherapy followed by allo-HSCT is ongoing (JCOG0907).

New agents for ATL

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 [38].

Other purine analogs clinically studied for ATL are fludarabine and cladribine. Fludarabine is a standard treatment for B-cell chronic lymphocytic leukemia and other lymphoid malignancies. In a phase I study of fludarabine in Japan in which 5 ATL patients and 10 B-CLL patients with refractory or relapsed-disease were enrolled [54], 6 grade 3 non-hematological toxic events were observed among the ATL patients. A PR was achieved only in one of the 5 ATL patients and the duration was short. Cladribine is among the 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 [55].

Histone deacetylase inhibitor

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. Several classes of HDAC inhibitor (HDACI) have been found to have potent anticancer effects in preclinical studies. HDACIs such as vorinostat (suberoylanilide hydroxamic acid; SAHA), romidepsin (depsipeptide) and panobinostat (LBH589) have also shown promise in preclinical and/or clinical studies against T-cell malignancies including ATL [56]. 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 [54]. However, a phase II study for CTCL and indolent ATL in Japan 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

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 chemokine receptor 4 (CCR4), have shown promise in 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 [57]. 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 interleukin-2 receptor (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 responses lasted longer than that obtained with unconjugated anti-Tac antibody [58,59].

Siplizumab is a humanized MoAb targeting CD2 and showed efficacy in a murine ATL model. Phase I dose-escalating study of this agent in 22 patients with several kinds of T/NK-cell malignancy revealed six responses (two CR in large granulocyte lymphocyte [LGL] leukemia, three PR in ATL and one PR in CTCL). However, four patients developed EBV-associated lymphoproliferative disorder (LPD) [60]. The broad specificity of this agent may eliminate both CD4- and CD8-positive T cells as well as NK cells without effecting B cells and predispose individuals to the development of EBV LPD.

CC chemokine receptor 4 (CCR4) is expressed on normal T helper type and regulatory T (Treg) cells and on certain types of T-cell neoplasms [17]. KW-0761, a humanized anti-CCR4 MoAb, with a defucosylated Fc region, exerts strong antibody-dependent cellular cytotoxicity (ADCC) due to increased binding to the Fcγ receptor on effecter cells. 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 three PTCL) revealed that one patient, at the maximum dose (1.0 mg/kg), developed grade (G) 3 dose-limiting toxic effects, namely skin rashes and febrile neutropenia, and G4 neutropenia [61]. Other treatment-related G3-4 adverse events 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: 2 complete (0.1; 1.0 mg/kg) and 3 partial (0.01; 2 at 1.0 mg/kg) responses. Three out of 13 patients with ATL (31%) achieved a response (2 CR and 1 PR). Responses in each lesion were diverse, i.e. good in PB (6 CR and 1 PR/7 evaluable cases), intermediate in skin (3 CR and 1 PR/8 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.

A subsequent phase II study of the agent given once per week for 8 weeks at 1.0 mg/kg to patients with relapsed, aggressive CCR4-positive ATL was conducted [62]. Objective responses were noted in 13 of 26 evaluable patients, including eight CRs, with an overall response rate of 50% (95% CI, 30%–70%). Median progression-free and overall survival were 5.2 and 13.7 months, respectively. The most common adverse events were Lymphocytopenia (95%), infusion reactions (89%) and skin rashes (63%), which

were manageable. Based on the results, this agent was approved by the Ministry of Health, Labor and Welfare in Japan. Further investigation of KW-0761 for treatment of ATL and other T-cell neoplasms is ongoing including a randomized phase II trial of VCAP-AMP-VECP (mLSG15) ± mogamulizumab for untreated aggressive ATL.

Other agents

Lenalidomide is an immunomodulatory agent, and was approved for multiple myeloma and myelodysplastic syndromes associated with 5q deletions. Recently, a phase I study of lenalidomide in patients with relapsed advanced ATL or PTCL was conducted in Japan [63]. Based on the development of two DLTs (platelets <10,000/uL and Grade 3 fatigue in one patient and Grade 3 prolongation of QTc interval in one patient), 25 mg daily per 28-day cycle was regarded as the MTD. Among the nine ATL patients, three achieved partial responses (PR) with a hematological complete response in two patients, including the disappearance of skin lesions in one patient. Among the four PTCL patients, one achieved a PR. Based on the preliminary evidence of antitumor activity in ATL patients, a phase II study in patients with relapsed ATL has been started in Japan.

Bortezomib, a proteasome inhibitor, that has exhibited preclinical and clinical activity against T-cell malignancies including ATL, is now under clinical trials for relapsed ATL in Japan [64]. Other potential drugs for ATL include, pralatrexate, a new agent with clinical activity in T-cell malignancies including ATL [65,66]. Pralatrexate is a novel anti-folate with improved membrane transport and polyglutamylation in tumor cells and high affinity for the reduced folate carrier (RFC) highly expressed in malignant cells, and was approved by the FDA for peripheral T-cell lymphoma in 2009.

Prevention

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. For several decades, before initiation of the interventions, the prevalence of HTLV-1 had declined drastically in endemic areas in Japan, probably because of birth cohort effects [13]. The elimination of HTLV-1 in endemic areas is now considered possible due to the natural decrease in the prevalence as well as intervention of transmission through blood transfusion and 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 as described above [15]. Also, no agent has been found to be effective in preventing the development of ATL among HTLV-1 carriers.

Conflict of interest

Kunihiro Tsukasaki received research grants from Celgene and Mundipharma.

Kensei Tobinai received research grants from Merck, Celgene, Kyowa-Kirin, Janssen Pharmaceuticals, and Mundipharma.

Role of the funding source

This work was supported in part by the National Cancer Center Research and Development Fund (23-A-17).

References

[1] Uchiyama T, Yodoi J, Sagawa K, et al. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood 1977;50:481–92.

[2] Poiesz BJ, Ruscetti FW, Gazdar AF, et al. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci U S A 1980;77:7415–9.

[3] Hinuma Y, Nagata K, Hanaoka M, et al. Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci U S A 1981;78(10):6476–80.

[4] Miyoshi I, Kubonishi I, Yoshimoto S, et al. Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T cells. Nature 1981;294(5843):770–1.
[5] Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci U S A 1982;79:2031–5.
[6] Gessain A, Barin F, Vernant JC, et al. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet 1985;2(8452):407–10.
[7] Osame M, Usuku K, Izumo S, et al. HTLV-I associated myelopathy, a new clinical entity. Lancet 1986;1(8488):1031–2.
[8] Mochizuki M, Watanabe T, Yamaguchi K, et al. HTLV-I uveitis: a distinct clinical entity caused by HTLV-I. Jpn J Cancer Res 1992;83(3):236–9.
[9] LaGrenade L, Hanchard B, Fletcher V, et al. Infective dermatitis of Jamaican children: a marker for HTLV-I infection. Lancet 1990;336(8727):1345–7.
[10] Takatsuki K. Adult T-cell leukemia. Oxford: Oxford University Press, New York; 1994.
[11] Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma: a report from the Lymphoma Study Group (1984–87). Br J Haematol 1991;79:428–37.
[12] Tajima K., T- and B-cell Malignancy Study Group. The 4th nationwide study of adult T-cell leukemia/lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. Int J Cancer 1990;45:237–43.
[13] Satake M, Yamaguchi K, Tadokoro K. Current prevalence of HTLV-1 in Japan as determined by screening of blood donors. J Med Virol 2012;84(2):327–35.
[14] Hisada M, Okayama A, Shioiri S, et al. Risk factors for adult T-cell leukemia among carriers of human T-lymphotropic virus type I. Blood 1998;92(10):3557–61.
[15] Iwanaga M, Watanabe T, Utsunomiya A, et al. Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: a nationwide prospective study in Japan. Blood 2010;116(8):1211–9.
[16] Satou Y, Yasunaga J, Yoshida M, et al. HTLV-1 basic leucine zipper factor gene mRNA supports proliferation of adult T cell leukemia cells. Proc Natl Acad Sci U S A 2006;103:720–5.
[17] Ishida T, Utsunomiya A, Iida S, et al. Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. Clin Cancer Res 2003;9:3625–34.
[18] Tsukasaki K, Tsushima H, Yamamura M, et al. Integration patterns of HTLV-1 provirus in relation to the clinical course of ATL: frequent clonal change at crisis from indolent disease. Blood 1997;89:948–56.
[19] Wattel E, Vartanian JP, Pannetier C, et al. Clonal expansion of human T-cell leukemia virus type I-infected cells in asymptomatic and symptomatic carriers without malignancy. J Virol 1995 May;69(5):2863–8.
[20] Yamagishi M, Nakano K, Miyake A, et al. Polycomb-mediated loss of miR-31 activates NIK-dependent NF-κB pathway in adult T cell leukemia and other cancers. Cancer Cell. 2012;21(1):121–35.
[21] Fujimoto T, Hata T, Itoyama T, et al. High rate of chromosomal abnormalities in HTLV-I-infected T-cell colonies derived from prodromal phase of adult T-cell leukemia: a study of IL-2-stimulated colony formation in methylcellulose. Cancer Genet Cytogenet 1999;109(1):1–13.
[22] Tawara M, Hogerzeil SJ, Yamada Y, et al. Impact of p53 aberration on the progression of adult T-cell leukemia/lymphoma. Cancer Lett 2006;234:249–55.
[23] Tsukasaki K, Krebs J, Nagai K, et al. Comparative genomic hybridization analysis in adult T-cell leukemia/lymphoma: correlation with clinical course. Blood 2001;97(12):3875–81.
[24] Choi YL, Tsukasaki K, O'Neill MC, et al. A genomic analysis of adult T-cell leukemia. Oncogene 2007 Feb 22;26(8):1245–55.
[25] Sasaki H, Nishikata I, Shiraga T, et al. Overexpression of a cell adhesion molecule, TSLC1, as a possible molecular marker for acute-type adult T-cell leukemia. Blood 2005 Feb 1;105(3):1204–13.
[26] Ohshima K, Jaffe ES, Kikuchi M. Adult T-cell leukemia/lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., editors. WHO classification of tumour of haemaopoietic and lymphoid tissues. 4th ed. Lyon: IARC Press; 2008. p. 281–4.
[27] Bittencourt AL, da Graças Vieira M, Brites CR, et al. Adult T-cell leukemia/lymphoma in Bahia, Brazil: analysis of prognostic factors in a group of 70 patients. Am J Clin Pathol 2007;128:875–82.
[28] Amano M, Kurokawa M, Ogata K, et al. New entity, definition and diagnostic criteria of cutaneous adult T-cell leukemia/lymphoma: human T-lymphotropic virus type 1 proviral DNA load can distinguish between cutaneous and smoldering types. J Dermatol 2008;35(5):270–5.
[29] Sawada Y, Hino R, Hama K, et al. Type of skin eruption is an independent prognostic indicator for adult T-cell leukemia/lymphoma. Blood 2011;117(15):3961–7.
[30] Watanabe T, Yamaguchi K, Takatsuki K, et al. Constitutive expression of parathyroid hormone-related protein gene in human T cell leukemia virus type 1 (HTLV-1) carriers and adult T cell leukemia patients that can be trans-activated by HTLV-1 tax gene. J Exp Med 1990;172(3):759–65.
[31] Nosaka K, Miyamoto T, Sakai T, et al. Mechanism of hypercalcemia in adult T-cell leukemia: overexpression of receptor activator of nuclear factor kappaB ligand on adult T-cell leukemia cells. Blood 2002;99(2):634–40.
[32] Ikeda S, Momita S, Kinoshita K, et al. Clinical course of human T-lymphotropic virus type I carriers with molecularly detectable monoclonal proliferation of T lymphocytes: defining a low- and high-risk population. Blood 1993;82(7):2017–24.
[33] 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 2009;27:453–9.
[34] Lymphoma Study Group. Major prognostic factors of patients with adult T-cell leukemia-lymphoma: a cooperative study. Leuk Res 1991;15:81–90.
[35] Katsuya H, Yamanaka T, Ishitsuka K, et al. Prognostic index for acute- and lymphoma-type adult T-cell leukemia/lymphoma. J Clin Oncol 2012;30:1635–40.
[36] Fukushima T, Nomura S, Tsukasaki K, et al. Characterization of long term survivors and a predictive model for aggressive adult T-cell leukemia-lymphoma (ATL): an ancillary study by the Japan Clinical Oncology Group, JCOG0902A. Blood 2011;118:881 [abstract].
[37] Takasaki Y, Iwanaga M, Imaizumi Y, et al. Long-term study of indolent adult T-cell leukemia-lymphoma. Blood 2010;115(22):4337–43.

[38] Tsukasaki K, Tobinai K, Shimoyama M, et al. Deoxycoformycin-containing combination chemotherapy for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group study (JCOG9109). Int J Hematol 2003;77:164–70.
[39] Yamada Y, Tomonaga M, Fukuda H, et al. A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukemia-lymphoma (ATL): Japan Clinical Oncology Group (JCOG) Study 9303. Br J Haematol 2001;113:375–82.
[40] 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 2007;25:5458–564.
[41] Gill PS, Harrington W, Kaplan MH, et al. Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. N Engl J Med 1995;332:1744–8.
[42] Hermine O, Blouscary D, Gessain A, et al. Treatment of adult T-cell leukemia-lymphoma with zidovudine and interferon alfa. N Engl J Med 1995;332:1749–51.
[43] Tobinai K, Kobayashi Y, Shimoyama M, et al. Interferon alfa and zidovudine in adult T-cell leukemia-lymphoma (correspondence). N Engl J Med 1995;333:1285–6.
[44] Datta A, Bellon M, Sinha-Datta U, et al. Persistent inhibition of telomerase reprograms adult T-cell leukemia to p53-dependent senescence. Blood 2006 Aug 1;108(3):1021–9.
[45] Bazarbachi A, Plumelle Y, Ramos JC, et al. Meta-analysis on the use of zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. J Clin Oncol 2010;27:417–23.
[46] Hodson A, Crichton S, Montoto S, et al. Use of zidovudine and interferon alfa with chemotherapy improves survival in both acute and lymphoma subtypes of adult T-cell leukemia/lymphoma. J Clin Oncol 2011;29(35):4696–701.
[47] Kchour G, Tarhini M, Kooshyar M-M, et al. Phase 2 study of the efficacy and safety of the combination of arsenic trioxide, interferon alpha, and zidovudine in newly diagnosed chronic adult T-cell leukemia/lymphoma (ATL). Blood 2009;113: 6528–32.
[48] Hishizawa M, Kanda J, Utsunomiya A, et al. Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study. Blood 2010;116(8):1369–76.
[49] Kanda J, Hishizawa M, Utsunomiya A, et al. Impact of graft-versus-host disease on outcomes after allogeneic hematopoietic cell transplantation for adult T-cell leukemia: a retrospective cohort study. Blood 2012;119(9):2141–8.
[50] Okamura J, Utsunomiya A, Tanosaki R, et al. Allogeneic stem-cell transplantation with reduced conditioning intensity as a novel immunotherapy and antiviral therapy for adult T-cell leukemia/lymphoma. Blood 2005;105:4143–5.
[51] Choi I, Tanosaki R, Uike N, et al. Long-term outcomes after hematopoietic SCT for adult T-cell leukemia/lymphoma: results of prospective trials. Bone Marrow Transplant 2011;46(1):116–8.
[52] Ishida T, Hishizawa M, Kato K, et al. Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study. Blood 2012;120(8): 1734–41.
[53] Tamaki H, Matsuoka M. Donor-derived T-cell leukemia after bone marrow transplantation. N Engl J Med 2006 Apr 20; 354(16):1758–9.
[54] Arima N, Mizoguchi H, Shirakawa S, et al. Phase I clinical study of SH L573 (fludarabine phosphate) in patients with chronic lymphocytic leukemia and adult T-cell leukemia/lymphoma [Article in Japanese]. Gan To Kagaku Ryoho 1999;26(5):619–29.
[55] Tobinai K, Uike N, Saburi Y, et al. Phase II study of cladribine (2-chlorodeoxyadenosine) in relapsed or refractory adult T-cell leukemia-lymphoma. Int J Hematol 2003;77(5):512–7.
[56] Hasegawa H, Yamada Y, Tsukasaki K, et al. LBH589, a deacetylase inhibitor, induces apoptosis in adult T-cell leukemia/lymphoma cells via activation of a novel RAIDD-caspase-2 pathway. Leukemia 2011;25(4):575–87.
[57] Waldmann TA. Multichain interleukin-2 receptor: a target for immunotherapy in lymphoma. J Natl Cancer Inst 1989;81: 914–23.
[58] Waldmann TA, White JD, Carrasquillo JA, et al. Radioimmunotherapy of interleukin-2Ra-expressing adult T-cell leukemia with yttrium-90-labeled anti-Tac. Blood 1996;86:4063–75.
[59] Berkowitz JL, Janik JE, Stewart DM, et al. Phase II trial of daclizumab in human T-cell lymphotropic virus type-1 (HTLV-1)-associated adult T-cell leukemia/lymphoma (ATL). J Clin Oncol 2010;28:7s [suppl; abstr 8043].
[60] O'Mahony D, Morris JC, Stetler-Stevenson M, et al. EBV-related lymphoproliferative disease complicating therapy with the anti-CD2 monoclonal antibody, siplizumab, in patients with T-cell malignancies. Clin Cancer Res 2009;15(7):2514–22.
[61] Yamamoto K, Utsunomiya A, Tobinai K, et al. Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol 2010;28(9):1591–8.
[62] Ishida T, Joh T, Uike N, et al. Multicenter phase II study of KW-0761, a defucosylated anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma (ATL). Blood 2010;116:128a [abstract 285].
[63] Uike N, Ogura M, Imaizumi Y, et al. Multicenter phase 1 dose-escalation study of lenalidomide (CC-5013) in relapsed patients with advanced adult T-cell leukemia-lymphoma or peripheral T-cell lymphoma. Blood 2012;120:2737 [abstract].
[64] Satou Y, Nosaka K, Koya Y, et al. Proteasome inhibitor, bortezomib, potently inhibits the growth of adult T-cell leukemia cells both in vivo and in vitro. Leukemia 2004;18:1357–63.
[65] O'Connor Owen A, Pro Barbara, Pinter-Brown Lauren, et al. PROPEL: a multi-center phase 2 open-label study of pralatrexate (PDX) with vitamin B12 and folic acid supplementation in patients with replapsed or refractory peripheral T-cell lymphoma. Blood (ASH Annual Meeting Abstracts) 2008;112:261.
[66] Marneros AG, Grossman ME, Silvers DN, et al. Pralatrexate-induced tumor cell apoptosis in the epidermis of a patient with HTLV-1 adult T-cell lymphoma/leukemia causing skin erosions. Blood 2009;113(25):6338–41.

THE JOURNAL OF DERMATOLOGY

doi: 10.1111/j.1346-8138.2012.01639.x　*Journal of Dermatology* 2013; **40**: 2–14

GUIDELINE

Guidelines for the management of cutaneous lymphomas (2011): A consensus statement by the Japanese Skin Cancer Society – Lymphoma Study Group

Makoto SUGAYA,[1] Toshihisa HAMADA,[2] Kazuhiro KAWAI,[3] Kentaro YONEKURA,[4] Mikio OHTSUKA,[5] Takatoshi SHIMAUCHI,[6] Yoshiki TOKURA,[6] Koji NOZAKI,[7] Koji IZUTSU,[8] Ritsuro SUZUKI,[9] Mitsuru SETOYAMA,[10] Tetsuo NAGATANI,[11] Hiroshi KOGA,[12] Mamori TANI,[13] Keiji IWATSUKI[2]

[1]*Department of Dermatology, Faculty of Medicine, University of Tokyo, Tokyo,* [2]*Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama,* [3]*Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences,* [4]*Department of Dermatology, Imamura Bun-in Hospital, Kagoshima,* [5]*Department of Dermatology, Fukushima Medical University School of Medicine, Fukushima,* [6]*Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu,* [7]*Department of Gastrointestinal, Breast and Endocrine Surgery, The University of Tokyo Hospital,* [8]*Department of Hematology, Toranomon Hostapital, Tokyo,* [9]*Department of Hematopoietic Stem Cell Transplantation Data Management/Biostatistics, Nagoya University Graduate School of Medicine, Nagoya,* [10]*Department of Dermatology, Faculty of Medicine, University of Miyazaki, Miyazaki,* [11]*Department of Dermatology, Tokyo Medical University Hachioji Medical Center, Tokyo,* [12]*Department of Dermatology, School of Medicine, Shinshu University, Matsumoto, and* [13]*Department of Dermatology, Graduate School of Medicine, Osaka University, Osaka, Japan*

ABSTRACT

In 2010, the first Japanese edition of guidelines for the management of cutaneous lymphoma was published jointly by the Japanese Dermatological Association (JDA) and the Japanese Skin Cancer Society (JSCS) – Lymphoma Study Group. Because the guidelines were revised in 2011 based on the most recent data, we summarized the revised guidelines in English for two reasons: (i) to inform overseas clinicians about our way of managing common types of cutaneous lymphomas such as mycosis fungoides/Sézary syndrome; and (ii) to introduce Japanese guidelines for lymphomas peculiar to Asia, such as adult T-cell leukemia/lymphoma and extranodal natural killer/T-cell lymphoma, nasal type. References that provide scientific evidence for these guidelines have been selected by the JSCS – Lymphoma Study Group. These guidelines, together with the degrees of recommendation, have been made in the context of limited medical treatment resources, and standard medical practice within the framework of the Japanese National Health Insurance system.

Key words: adult T-cell leukemia/lymphoma, cutaneous lymphoma, guideline, mycosis fungoides, Sézary syndrome.

INTRODUCTION

A number of guidelines on the management of cutaneous lymphoma have already been published in Europe and North America. However, the prevalence and clinical types of cutaneous lymphoma vary among different ethnic groups, and medical systems vary from country to country. As a result, the unmodified European/US guidelines may not be well-suited for use in Japan. We wanted to provide a "best treatment" consensus on clinical practice guidelines for cutaneous lymphoma, based on the actual situation in Japan.

In these guidelines, the diagnosis of cutaneous lymphoma is based on classifications from the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer, Cutaneous Lymphomas Task Force (EORTC),[1] and on the 4th edition of the WHO classification published in 2008.[2] The staging and classification of mycosis fungoides (MF)/Sézary syndrome (SS) are based on the tumor

Correspondence: Keiji Iwatsuki, M.D., Ph.D., Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmoceutical Sciences, Okayama, 700-8558, Japan. Email: keijiiwa@cc.okayama-u.ac.jp

Conflict of interest: none

Received 22 June 2012; accepted 26 June 2012.

–node–metastasis (TNM) staging from the International Society for Cutaneous Lymphomas (ISCL) group.[3] For cutaneous lymphomas other than MF/SS, we decided to use the TNM staging system proposed by the ISCL[4] rather than the conventional Ann Arbor classification system.

The British group,[5] EORTC[6] and European Society for Medical Oncology (ESMO)[7] each issued treatment guidelines for MF/SS. In 2009, using published work and overseas guidelines for references, we published the first edition of guidelines based on the actual situation of cutaneous lymphoma in Japan.[8] Because the guidelines were revised in 2011 based on the most recent data, we summarized the revised guidelines in English for two reasons: (i) to inform overseas clinicians about our way of managing common types of cutaneous lymphomas such as MF/SS; and (ii) to introduce Japanese guidelines for lymphomas peculiar to Asia, such as adult T-cell leukemia/lymphoma and extranodal natural killer (NK)/T-cell lymphoma (ENKL), nasal type. References that provide scientific evidence for these guidelines have been selected by the Japanese Skin Cancer Society (JSCS) – Lymphoma Study Group. These guidelines, together with the degrees of recommendation, have been made in the context of limited medical treatment resources, and standard medical practice within the framework of the Japanese National Health Insurance system. The evidence level and degree of recommendation used for the current version are shown in Table 1.

BASIS FOR THE CURRENT GUIDELINES

The cutaneous lymphomas listed in the present guidelines are basically in accordance with the WHO–EORTC classification (2005),[1] but it is difficult to precisely define "primary cutaneous" lymphoma. Ordinarily, a condition is defined as "primary cutaneous" lymphoma if appropriate procedures show no extracutaneous lesions at the time of diagnosis. The present guidelines include lymphomas and hematopoietic malignancies with marked affinity for the skin (Fig. 1, Table 2). The diagnostic nomenclature follows the 4th edition of the WHO classification (2008).[2]

To describe the skin lesions of cutaneous lymphoma, typically MF/SS, uniform terminology is needed. Without consistent terminology, accurate disease staging is impossible, and inconsistencies may develop in prognostic analysis. The ISCL/EORTC group has defined terminology for MF/SS.[9] Those definitions are adopted in the present guidelines (Table S1), and representative clinicopathological findings of various types of cutaneous lymphoma are provided in supporting information (Figs S1–S7).

STAGING

Staging for MF/SS (ISCL/EORTC 2007, modified in 2011)

For the staging of MF/SS, we previously used the categories developed by Bunn *et al.*[10] and Sausville *et al.*[11] In 2007, a new staging system was proposed by the ISCL/EORTC group,[3] which was modified in 2011 (Tables S2 and S3).[12]

In the ISCL/EORTC staging system, peripheral blood findings are classified into three categories: B_0 (atypical lymphocytes accounting for $\leq 5\%$ of peripheral blood lymphocytes), B_1 (atypical lymphocytes accounting for >5% of peripheral blood lymphocytes, but <1000/μL), and B_2 (atypical lymphocyte

Table 1. Standards for the determination of evidence level and degree of recommendation

Classification of evidence level	
I	Systematic review and/or meta-analysis Staging/classification proposal and treatment recommendation or consensus paper from WHO, EORTC and ISCL
II	One or more randomized comparative studies
III	Non-randomized comparative studies
IV	Analytical epidemiology studies (cohort research and case–control studies) Case series studies (≥ 5 cases)
V	Descriptive studies (case reports and case series studies [<5 cases])
VI	Opinions of expert committee and individual specialists*
Degree of recommendation classification†	
A	Strongly recommended for implementation (efficacy shown by at least 1 report providing level I or high-quality level II evidence)
B	Recommended for implementation (efficacy shown by ≥ 1 reports providing low-quality level II, high-quality level III, or very high-quality level IV evidence)
B-C1	Recommended for implementation, but less strongly supported than B
C1	Implementation can be considered, but evidence‡ is insufficient (low-quality III–IV, high-quality multiple V, or committee-approved VI evidence)
C2	No evidence‡; cannot be recommended (no evidence of effectiveness, or evidence available of ineffectiveness)
D	Recommended not to implement (high-quality evidence of ineffectiveness or harmfulness)

*Data from basic research and theories derived from such data are placed at this level. †Some of the "degree of recommendation" statements in these guidelines are not in complete agreement with the above table. ‡"Evidence" refers to knowledge from clinical trials and epidemiological research. This is because these "degree of recommendation" grades were based on a consensus among the committee members, taking feasibility into account. This consensus was reached after due consideration of the shortage of evidence internationally on the treatment of skin cancer and the fact that the evidence from overseas is not directly applicable in Japan.

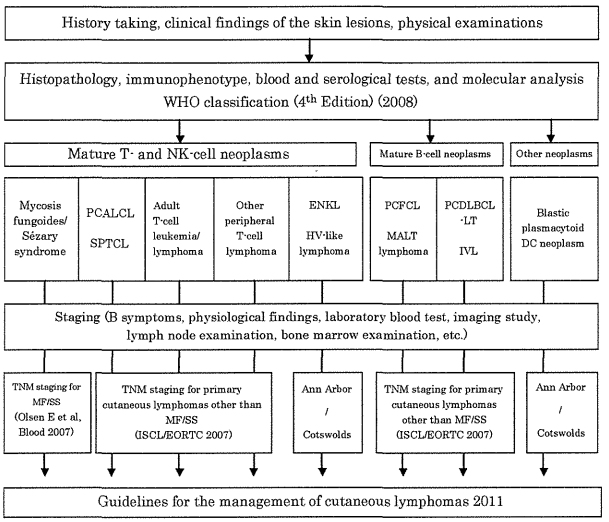

Figure 1. Diagnostic and staging algorithm for cutaneous lymphomas. DC, dendritic cell; ENKL, extranodal T/NK-cell lymphoma, nasal type; HV, hydroa vacciniforme; IVL, intravascular large B-cell lymphoma; MALT lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type; MF/SS, mycosis fungoides/Sézary syndrome; PCALCL, primary cutaneous anaplastic large cell lymphoma; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; PCFCL, primary cutaneous follicle center lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; TNM, tumor–node–metastasis; WHO, World Health Organization.

count of $\geq$1000/μL with a positive clone). Additional parameters that meet the B_2 criteria include the following: CD4/CD8 ratio of 10 or more, $CD4^+CD7^-$ of 40% or more, and $CD4^+CD26^-$ of 30% or more.[3,12,13] Cases with erythroderma who meet the B_2 criteria are defined as SS, or stage IVA_1 (Table S3 and Fig. S1). Erythrodermic MF of the B_0 or B_1 category is classified as stage IIIA or IIIB.

If lymphoma cells replace all or large portions of the lymph node structure, the condition is diagnosed as N_3 and is classified as stage IV_2 (Table S3). Even if the lymph node is infiltrated by atypical cells, a diagnosis of N_3 is not made as long as the foci are small and nodal architecture is preserved.[3,12]

TNM classification of cutaneous lymphoma other than MF/SS (ISCL/EORTC 2007)

No TNM classification appropriate for the evaluation of cutaneous lesions was available for primary cutaneous lymphoma categories other than MF/SS. In 2007, the ISCL and EORTC proposed a new TNM classification system (Table S4).[4] Although the TNM classification reflect the extent of lesions, an adequate staging system has not been established yet. Moreover, the classification does not indicate prognoses for some disease types.[14] The category of "non-MF/SS" covers many types of cutaneous lymphoma, and new staging systems are needed for each disease type, based on the collected clinical data and prognostic analysis.

Table 2. Classification of cutaneous lymphomas

Cutaneous T/NK cell lymphoma
Mycosis fungoides: MF
Variants
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome: SS
Adult T-cell leukemia/lymphoma
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Hydroa vacciniforme-like lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
Primary cutaneous $CD4^+$ small/medium T-cell lymphoma*
Peripheral T-cell lymphoma, not otherwise specified
Cutaneous B-cell lymphomas
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Hematological precursor cell neoplasm
Blastic plasmacytoid dendritic cell neoplasm

*Provisional. Representative clinicopathological features of MF/SS, anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, subcutaneous panniculitis-like T-cell lymphoma, extranodal NK/T cell lymphoma, hydroa vacciniforme-like lymphoma, blastic plasmacytoid dendritic cell neoplasm have been shown in Figs S1–S7.

Staging of other cutaneous lymphomas and hematopoietic malignancies

Shimoyama and colleagues have provided a widely-used classification of adult T-cell leukemia/lymphoma (ATLL): acute, lymphoma, chronic and smoldering types.[15] According to Shimoyama's criteria, ATLL patients with cutaneous lesions only are usually classified into the smoldering group. It is not appropriate to stage ATLL patients with the TNM system proposed by Kim *et al.*[4] because of the presence of minimal hematological disease. Furthermore, for other hematological malignancies such as ENKL, nasal type, and blastic plasmacytoid dendritic cell neoplasm, the Ann Arbor or Cotswolds staging (Table S5)[16] has been widely adopted in Japan because of hematological and extracutaneous spreading of the illness.

EPIDEMIOLOGY OF CUTANEOUS LYMPHOMA

In line with the WHO classification (3rd edn), the incidence of all types of lymphomas was reported by pathologists in Japan.[17] The data were distinct from those in Western countries and similar in several ways to other data from Asia, although the relatively high rate of ATLL was attributed to the geographical difference in the etiologic factor, human T-lymphotropic virus

type 1 (HTLV-1). The JSCS – Lymphoma Study Group has conducted a nationwide survey of cutaneous lymphoma annually since 2007 (www.okayama-hihuka.jp/pdf/kekka2010.pdf). MF/SS account for approximately 51% of all cutaneous lymphomas, followed by ALCL and ATLL at approximately 9–8% each. B-cell lymphoma accounts for approximately 15% of all cutaneous lymphoma in Japan, so it is less frequent than in Europe or North America. ENLK, nasal type, accounts for only approximately 2%, which is nearly always associated with Epstein–Barr virus (EBV) infection. The NK-cell type is dominant in Japan.

PROGNOSTIC ANALYSIS

Prognostic analyses of patients with cutaneous lymphoma are limited.[18–21] In the present guidelines, we have highlighted the prognoses of MF/SS, ATLL, and ENLK, nasal type, the latter two of which preferentially occur in Japan. For the other types of cutaneous lymphoma, we have used reports from other countries (Table 3).[22–26]

MF/SS

Previous researchers already contributed to disease staging and prognostic analysis for MF/SS.[27] Since the new staging was advocated in 2007, prognostic analyses have been reported from Japan and the UK (Table 3).[18,22] The survival rates of Japanese patients with MF/SS were similar to those shown in previous studies conducted in the USA and Europe. The prognoses of patients with skin tumor (stage IIB) and extracutaneous involvement (stage IV) were significantly worse than those of patients with early-stage disease (stages IA–IIA). Erythrodermic MF patients without blood involvement (stage IIIA) showed excellent survival. Independent prognostic factors in multivariate analyses were higher age and the presence of either skin tumor or extracutaneous disease.[18] Although findings in Japan showed the prognosis for stage IIIA to be quite favorable, a British analysis indicated that it was similar to the prognosis for stage IIb,[22] this may have occurred because the two reports did not use the same diagnostic criteria for erythrodermic lymphoma, resulting in differences in patient characteristics.

ATLL

A recent observation in Japan indicated that the patch and plaque types of ATLL were associated with better survival rates.[19] Multivariate analysis demonstrated that the hazard ratios of the erythrodermic and nodulotumoral types were significantly higher than that of the patch type, and that the eruption type is an independent prognostic factor for ATLL. The overall survival worsened as the T stage became more advanced: the multipapular type and T2 were comparable, and the purpuric type had a significantly poorer prognosis than T1 (Fig. S3).[19]

ENKL

Suzuki *et al.*[20] have reported the prognosis of a total 150 patients with ENKL, nasal type, consisting of 123 nasal and 27 extranasal (16 cutaneous, nine hepatosplenic, one intestinal and one nodal) lymphomas. We focused on patients with the cutaneous type of ENKL, and re-examined their prognoses. Patients with stage I disease (determined by the Ann Arbor staging system) showed a favorable prognosis in 5-year overall survival of 75%, but the prognoses deteriorated in the advanced stages (Table 3). Unlike a previous study on $CD56^+$ hematological neoplasms with or without EBV infection in Europe,[28] our data highlighted that ENKL is usually associated with EBV infection, and assessed the prognoses of "nasal" and "cutaneous" ENKL separately.

TREATMENT GUIDELINES

Treatment guidelines for MF/SS

Mycosis fungoides/Sézary syndrome is the oldest defined form of cutaneous lymphoma, and is more common than other primary cutaneous lymphomas (Tables 4–11). At present, no treatment based on high-level evidence is available for this condition. In many cases, the clinical course may extend for 10 years or more. Therefore, the success or failure of therapeutic intervention may be difficult to determine. Moreover, ethical issues may complicate the implementation of randomized placebo-controlled studies. Only four randomized studies have compared the effectiveness of different treatment methods[29–32] and only one randomized placebo-controlled study has been conducted.[33] These guidelines give substantial weight to consensus among the committee members. The "B" recommendation level has been given to first-line therapies for daily clinical practice.

An additional problem is that far fewer treatment options are available for MF/SS in Japan than in Western countries. In the present guidelines, we have included information on treatment modalities that have not been approved by the Japanese National Health Insurance system. Experimental therapies not yet approved overseas or in Japan have been omitted from these guidelines.

CQ1: Is monitoring the clinical course without treatment recommended for MF?
Degree of recommendation: C1 (stage IA only), C2 (other than stage IA).
Recommendation: In stage IA of MF, one acceptable option is to monitor the clinical course without treatment. For stages beyond IA, monitoring the clinical course without treatment is generally not recommended (Data S1).

CQ2: Are topical steroids recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Topical steroid therapy is recommended at all stages of MF/SS (Data S1).

CQ3: Is topical chemotherapy recommended for MF/SS?
Degree of recommendation: C1.
Recommendation: Mechlorethamine/nitrogen mustard (HN2) or carmustine (BCNU) topical chemotherapy is currently used in Europe and North America, and is recommended for early-stage MF (stage IA through IIA). These agents are not yet approved or available in Japan. Nimustine hydrochloride (ACNU) is currently used topically in some facilities in Japan,

Table 3. Survival rates of various cutaneous lymphomas and hematological neoplasms

Disease	Stage	5y-OS	5y-DSS	Median survival time (months)	References
MF/SS	IA	94–100	98–100	426	18, 22
	IB	84–89	89–95	258	
	IIA	78–87	87–89	190	
	IIB	47–73	56–88	56–78	
	IIIA	47–100	54–100	56	
	IIIB	40	48	41	
	IVA1	0–37	0–41	23–46	
	IVA2	18–33	23–50	25–46	
	IVB	0–18	0–18	13–17	
ATLL	T1	82.5	82.5	192.6*	19, 23
	T2	27.3	27.3	47.9	
	T3	0	0	17.3	
	T4	0	0	3	
	Multi-papular type	42.1	47.1		
	Purpuric type	40.0	40.0		
ALCL	T1	85	93		24
	T2	81	93		
	T3	63	77		
	Leg (−)	86	100		
	Leg (+)	53	67		
SPTCL	HPS (−)	91			25
	HPS (+)	45			
		Total 82			
Nasal ENKL	I	55 (4 years)		59.8	20
	II	33 (4 years)		11.2	
	III	31 (4 years)		33.1	
	IV	10 (4 years)		5.3	
		Total 36 (4 years)		Total 12.9	
Cutaneous extranasal ENKL	I	75 (2 years)		Not reached	20
	II	0 (2 years)		6.2	
	III	Not reached†		75.5†	
	IV	14 (2 years)		4	
		Total 33 (2 years)		Total 6.8	
BNKL	BM/blood (−)	0	25.3 (2 years)	17.1	21
	BM/blood (+)	19.6	46.4 (2 years)	20.4	
	Skin (−)	0	21 (2 years)	24.2	
	Skin (+)	20	48 (2 years)	22.2	
Extranodal MZL of MALT		94–97			26, 27
PCFCL		87–96			
PCDLBCL		37–73			

*Mean survival time. †One case. ALCL, anaplastic large cell lymphoma; ATLL, adult T cell leukemia/lymphoma; BM, bone marrow; BNKL, blastic NK-cell lymphoma; DSS, disease-specific survival; ENKL, extranodal NK/T-cell lymphoma; HPS, hemophagocytic syndrome; MF, mycosis fungoides; MZL of MALT, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; OS, overall survival; PCDLBCL, primary cutaneous diffuse large B-cell lymphoma; PCFCL, primary cutaneous follicle center lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; SS, Sezary syndrome.

and can be considered for small skin lesions or for short-term use (Data S1).

CQ4: Is ultraviolet (UV) light therapy recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Oral psoralen plus UV-A therapy (PUVA) therapy or narrow-band UV-B therapy is recommended for early-stage MF (stage IA through IIA) (Data S1).

CQ5: Is PUVA therapy with concomitant retinoid or interferon (IFN) therapy recommended for MF/SS?
Degree of recommendation: B.
Recommendation: PUVA with concomitant oral etretinate (RePUVA) or PUVA with concomitant IFN is recommended for MF/SS (Data S1).

CQ6: Is radiation therapy recommended for MF/SS?
Degree of recommendation: B.
Recommendation: Localized radiation therapy is recommended as a palliative treatment for skin lesions in MF, regardless of disease stage. Total skin electron beam therapy is recommended for MF (stage IB through IIA) (Data S1).

CQ7: Are oral retinoids recommended for MF/SS?
Degree of recommendation: B-C1.

Table 4. Summary of clinical questions and degree of recommendation for mycosis fungoides/Sézary syndrome

Clinical question	Degree of recommendation
CQ1: Is monitoring the clinical course without treatment recommended for mycosis fungoides?	C1 (stage IA) C2 (other than stage IA)
CQ2: Are topical steroids recommended for mycosis fungoides/Sézary syndrome?	B
CQ3: Is topical chemotherapy recommended for mycosis fungoides/Sézary syndrome?	C1
CQ4: Is ultraviolet light therapy recommended for mycosis fungoides/Sézary syndrome?	B
CQ5: Is psoralen plus ultraviolet A therapy with concomitant retinoid or interferon therapy recommended for mycosis fungoides/Sézary syndrome?	B
CQ6: Is radiation therapy recommended for mycosis fungoides/Sézary syndrome?	B
CQ7: Are oral retinoids recommended for mycosis fungoides/Sézary syndrome?	B-C1
CQ8: Is interferon therapy recommended for mycosis fungoides/Sézary syndrome?	B-C1
CQ9: Is extracorporeal photochemotherapy recommended for mycosis fungoides/Sézary syndrome?	B (erythroderma) C1 (non-erythroderma)
CQ10: Are molecular-targeted therapies recommended for mycosis fungoides/Sézary syndrome?	B-C1
CQ11: Is chemotherapy recommended for mycosis fungoides/Sézary syndrome?	B (refractory, extracutaneous lesions) D (early stage)
CQ12: Is hematopoietic stem cell transplantation recommended for mycosis fungoides/Sézary syndrome?	C1 (allogeneic) C2 (autologous)

Table 5. (MF/SS-1) Topical therapy of first choice recommended for stages I and IIA*

Treatment	Degree of recommendation	CQ
Monitoring the clinical course without treatment	C1 (stage IA only)/C2	CQ1
Topical steroid therapy†	B	CQ2
ACNU topical therapy‡	C1	CQ3
BB-UVB†	B	CQ4
NB-UVB	B	CQ4
PUVA	B	CQ4
Localized radiation therapy§	B	CQ6

*If the patient does not respond to the topical therapy selected for initial treatment, before proceeding to a second-line therapy recommended for stage I through IIA (Table 6 MFSS-2), consider the use of other first-line topical therapies. †Stage IA/IB. ‡Small area, short-term use. §Radical radiation therapy for "minimal" stage IA unilesional mycosis fungoides, or where multiple lesions are localized within the same radiation field or multiple field in close proximity, and palliative radiation for infiltrated plaques resistant to topical therapy other than radiation. ACNU, nimustine hydrochloride; BB, broad-band; NB, narrowband; PUVA, psoralen plus ultraviolet A therapy; UVB, ultraviolet B.

Recommendation: Oral etretinate can be useful in the treatment of MF/SS (Data S1).

CQ8: Is IFN therapy recommended for MF/SS?
Degree of recommendation: B-C1.

Recommendation: IFN-α therapy is recommended in early-stage MF/SS (stage IA–IIA) if systemic therapy is required, and in advanced disease (stage IIB–IVA1). This treatment option has not yet been approved in Japan. IFN-γ, which has been used for the treatment of MF in Japan, is considered as effective as IFN-α, and may prove useful (Data S1).

Table 6. (MF/SS-2) Second-line therapy recommended for stages I and IIA

Treatment	Degree of recommendation	CQ
TSEB*	B	CQ6
Etretinate†,‡	B-C1	CQ7
IFN-α†,§	B-C1	CQ8
IFN-γ†	B-C1	CQ8
RePUVA†	B	CQ5
IFN-α + PUVA †,§	B	CQ5
IFN-γ + PUVA †	B	CQ5
Chemotherapy¶	D/B¶	CQ11

*TSEB can be used as first-line therapy for stage IB/IIA (T2) with intense subjective symptoms accompanied by extensive highly infiltrated plaques and histopathological confirmation of folliculotropic mycosis fungoides or large cell transformation. †Can be a first-line treatment if systemic therapy is required (B1 or histopathological confirmation of folliculotropic mycosis fungoides or large cell transformation). BRM therapy (etretinate, IFN-α, IFN-γ) can be used as monotherapy or in concomitant administration with PUVA, and its concomitant use can also be investigated with topical therapies other than PUVA. ‡Duration of response to oral etretinate is usually short; consider for use as concomitant therapy. §IFN-α therapy has been used in only a few cases in Japan. ¶Third-line therapy for stage IB/IIA disease resistant to skin-targeted therapy and BRM therapy. BRM, biological response modifiers; IFN, interferon; PUVA, psoralen plus ultraviolet A therapy; TSEB, total skin electron beam.

CQ9: Is extracorporeal photochemotherapy (ECP) recommended for MF/SS?
Degree of recommendation: B (erythrodermic MF/SS), C1 (non-erythrodermic disease).

Recommendation: ECP/photopheresis is recommended for stage T4 erythrodermic MF and SS. It may also be considered in cases of refractory non-erythrodermic MF. ECP is

Table 7. (MF/SS-3) First-line therapy recommended for stage IIB*

Treatment	Degree of recommendation	CQ
Concomitant use of the following forms of BRM therapy and topical therapy		
BRM therapy		
Etretinate	B-C1	CQ5,7
IFN-α†,‡	B-C1	CQ5,8
IFN-γ‡	B-C1	CQ5,8
Topical therapy		
PUVA ± localized radiation therapy§	B	CQ4,5,6
Localized radiation therapy§	B	CQ6
TSEB¶	B	CQ6

*If the patient does not respond to initial treatment, before proceeding to a second-line therapy recommended for refractory stage IIB (Table 8 MFSS-4), consider other first-line topical therapies. †Concomitant therapy with IFN-α and PUVA: degree of recommendation = B. IFN-α therapy has been used in only a few cases in Japan. ‡IFN-α monotherapy or IFN-γ monotherapy can be used as first-line therapy. §Palliative radiation for localized tumors. ¶If lesions extend over <10% of body surface area, TSEB monotherapy can be used as first-line therapy. BRM, biological response modifiers; IFN, interferon; PUVA, psoralen plus ultraviolet A therapy; TSEB, total skin electron beam.

Table 8. (MF/SS-4) Treatment methods recommended for refractory stage IIB/III or stage IV mycosis fungoides

Treatment	Degree of recommendation	CQ
Chemotherapy*	B	CQ11

*Consider concomitant use of topical therapy appropriate for T classification.

Table 9. (MF/SS-5) First-line therapy recommended for stage III *

Treatment	Degree of recommendation	CQ
ECP ± IFN-α†	B	CQ9
TSEB + ECP†,‡	B	CQ6
Concomitant use of the following forms of BRM therapy and topical therapy		
BRM therapy		
Etretinate	B-C1	CQ5,7
IFN-α†,§	B-C1	CQ5,8
IFN-γ§	B-C1	CQ5,8
Topical therapy		
PUVA	B	CQ4,5
TSEB§	B	CQ6

*If the patient does not respond to initial therapy, before proceeding to a therapy recommended for refractory stage III (Table 8 MFSS-4), consider other first-line therapies. †ECP and IFN-α therapy have been used in only a few cases in Japan. ‡TSEB monotherapy can be used as first-line therapy for stage IIIA disease. §IFN-α monotherapy or IFN-γ monotherapy can be used as first-line therapy. BRM, biological response modifiers; ECP, Extracorporeal photochemotherapy; IFN, interferon; PUVA, psoralen plus ultraviolet A therapy; TSEB, total skin electron beam.

Table 10. (MF/SS-6) Recommended therapy for Sézary syndrome (stage T4, IVA1-IVB)*

Treatment	Degree of recommendation	CQ
ECP ± IFN-α†	B	CQ9
TSEB + ECP†	B	CQ6
Chemotherapy ± IFN-α†	B	CQ11

*For stage IVA1 Sézary syndrome with a low Sézary cell count, initial therapy selection may be the same as for stage IIIB (Table 9 MF/SS-5). †ECP and IFN-α therapy have been used in only a few cases in Japan. ECP, extracorporeal photochemotherapy; IFN, interferon; TSEB, total skin electron beam.

Table 11. (MF/SS-7) Treatment to be considered for refractory stage IV disease

Treatment	Degree of recommendation	CQ
Allogeneic hematopoietic stem cell transplantation	C1	CQ12
Autologous hematopoietic stem cell transplantation	C2	CQ12

not yet approved by the Japanese National Health Insurance system, and currently almost no Japanese medical institutions perform the procedure (Data S1).

CQ10: Are molecular-targeted therapies recommended for MF/SS?
Degree of recommendation: B-C1.
Recommendation: Treatment with denileukin diftitox, vorinostat or romidepsin may be useful in recurrent or refractory MF/SS. Vorinostat is the only drug in this category that is approved for coverage by Japanese health insurance (Data S1).

CQ11: Is chemotherapy recommended for MF/SS?
Degree of recommendation: B (if disease is refractory or accompanied by extracutaneous lesions), D (early-stage MF).
Recommendation: Chemotherapy is not recommended as a first line of treatment in early-stage MF (stage IA–IIA). Chemotherapy is recommended for MF/SS stage IB–IIIB that is resistant to topical therapy or biological response modifier therapy, and for MF/SS stage IVA1–IVB accompanied by extracutaneous lesions (Data S1).

CQ12: Is hematopoietic stem cell transplantation recommended for MF/SS?
Degree of recommendation: C1 (allogeneic hematopoietic stem cell transplantation), C2 (autologous hematopoietic stem cell transplantation).
Recommendation: Autologous hematopoietic stem cell transplantation with concomitant high-dose chemotherapy is not generally recommended for MF/SS. In young patients with advanced disease, allogeneic hematopoietic stem cell transplantation may be considered in the context of a clinical study (Data S1).

Cutaneous T/NK-cell lymphoma other than MF/SS (non-MF/SS)

Cutaneous T/NK cell lymphomas other than MF/SS are classified by WHO–EORTC into two broad categories: relatively aggressive lymphomas with poor prognosis (aggressive group), and indolent lymphomas with favorable prognosis (indolent group) (Table 12).[1,34–39] In patients with aggressive lymphomas including primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma, primary cutaneous γδ T-cell lymphoma, and peripheral T-cell lymphoma, not otherwise specified, the 5-year survival rates are less than 20%. However, the clinical course is not uniform, and patients whose symptoms are limited to cutaneous lesions may live for much longer.

For patients who present with cutaneous lesions only, without general symptoms or notable laboratory test findings, skin-directed therapies used for MF/SS might be chosen as a first-line treatment. Systemic chemotherapy may be considered for patients with tumor infiltration into the lymph nodes or visceral organs. However, the best treatment option must be explored for each individual patient, based on that patient's conditions. Clinical questions (CQ) are not defined in this category because uniform guidelines are difficult to develop. In contrast, CQ have been defined in each lymphoma in the indolent group (primary cutaneous anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and primary cutaneous $CD4^+$ small/medium T-cell lymphoma).

The MF/SS staging classifications are not applicable to cutaneous T/NK cell lymphomas other than MF/SS because of differences in disease progression. In 2007, the ISCL and EORTC jointly advocated the TNM classification system for cutaneous lymphomas other than MF/SS.[4] Because the prognostic impact of this classification system has not yet been validated, it might be premature to establish guidelines based on it. However, no other applicable classification systems are available at the present time. In order to obtain clinical information based on common criteria, we have adopted the TNM classification in the present guidelines.

Primary cutaneous anaplastic large cell lymphoma.

CQ13: Are localized therapies such as radiation therapy or surgical resection recommended for primary cutaneous anaplastic large cell lymphoma?
Degree of recommendation: B.
Recommendation: Remission can be induced by radiation therapy or surgical resection in many patients, so these methods are recommended where feasible (Data S1).

CQ14: Is chemotherapy recommended for primary cutaneous anaplastic large cell lymphoma?
Degree of recommendation: B (for lymph node lesions and visceral organ infiltration), C1 (symptoms limited to cutaneous lesions only).
Recommendation: For patients with cutaneous lesions only, if those lesions are resistant to topical treatment such as radiotherapy and surgical excision, or if they have multiple lesions, chemotherapy may be considered. Chemotherapy is recommended for lymph node lesions and for infiltration in the visceral organs (Data S1).

Subcutaneous panniculitis-like T-cell lymphoma.

CQ15: Is radiation therapy recommended for subcutaneous panniculitis-like T-cell lymphoma?
Degree of recommendation: C1.
Recommendation: Radiation therapy can provide control of localized lesions within the irradiated area. Radiation can be considered as initial therapy for skin lesions within a localized area (T1, T2) without systemic symptoms (Data S1).

CQ16: Are oral steroids recommended for subcutaneous panniculitis-like T-cell lymphoma?
Degree of recommendation: B.
Recommendation: Steroid monotherapy has been reported to relieve systemic symptoms such as pyrexia and abnormal hepatic function and to induce remission in some cases; oral steroids are recommended for subcutaneous panniculitis-like T-cell lymphoma (Data S1).

Table 12. Summary of CQ and degree of recommendation for cutaneous T-/natural killer cell lymphoma (non-MF/SS)

Clinical question	Degree of recommendation
CQ13: Are localized therapies such as radiation therapy B or surgical resection recommended for primary cutaneous anaplastic large cell lymphoma?	B
CQ14: Is chemotherapy recommended for primary cutaneous anaplastic large cell lymphoma?	B (extracutaneous lesions) C1 (cutaneous lesions only)
CQ15: Is radiation therapy recommended for subcutaneous panniculitis-like T-cell lymphoma?	C1
CQ16: Are oral steroids recommended for subcutaneous panniculitis-like T-cell lymphoma?	B
CQ17: Is combination chemotherapy recommended for subcutaneous panniculitis-like T-cell lymphoma?	B-C1
CQ18: Is radiation therapy recommended for primary cutaneous $CD4^+$ small/medium T-cell lymphoma?	B
CQ19: Is chemotherapy recommended for primary cutaneous $CD4^+$ small/medium T-cell lymphoma?	C1

CQ17: Is combination chemotherapy recommended for subcutaneous panniculitis-like T-cell lymphoma?
Degree of recommendation: B-C1.
Recommendation: Combination chemotherapy may be considered if the condition is resistant to steroid therapy. Prognosis is poor for patients complicated by hemophagocytosis; combination chemotherapy is recommended in such cases (Data S1).

Primary cutaneous CD4$^+$ small/medium T-cell lymphoma.

CQ18: Is radiation therapy recommended for primary cutaneous CD4$^+$ small/medium T-cell lymphoma?
Degree of recommendation: B.
Recommendation: Radiation therapy can induce remission in many cases, and survival rates are relatively good. Radiation therapy is recommended for single and localized lesions (T1, T2) (Data S1).

CQ19: Is chemotherapy recommended for primary cutaneous CD4$^+$ small/medium T-cell lymphoma?
Degree of recommendation: C1.
Recommendation: Chemotherapy can also be considered for primary cutaneous CD4$^+$ small/medium T-cell lymphoma with multiple lesions (Data S1).

ATLL (disease type limited to cutaneous lesions)

Adult T-cell leukemia/lymphoma is a form of T-cell lymphoma caused by HTLV-1 which occurs in a variety of organs (Table 13). Three major findings required for diagnosis: (i) appearance of morphologically abnormal T lymphocytes (typically CD4$^+$ and CD25$^+$); (ii) seropositivity for anti-HTLV-1 antibody; and (iii) Southern blot confirmation for monoclonal integration of HTLV-1 provirus into tumor cells.[15,40] For cutaneous symptoms to be diagnosed as eruptions specific to ATLL, histological confirmation is required for (i) and (iii). In particular, (iii) is required for a differential diagnosis to exclude other cutaneous lymphomas such as MF. The overall treatment guidelines for ATLL must involve cooperation and coordination with other departments, including departments of hematology and oncology. Thus, we limit these guidelines to instances in which only cutaneous lesions are detected. However, no uniform diagnostic criteria exist for the conventionally advocated concept of "cutaneous" ATLL.[40–43] The present guidelines cover ATLL cases, where systemic treatments such as chemotherapy and transplantation are not indicated.

Table 13. Summary of CQ and degree of recommendation for adult T-cell leukemia/lymphoma (ATLL) with cutaneous lesions only

Clinical question	Degree of recommendation
CQ20: Is ultraviolet light therapy recommended for ATLL with cutaneous lesions only?	B-C1
CQ21: Is radiation therapy recommended for ATLL with cutaneous lesions only?	B
CQ22: Are oral retinoids recommended for ATLL with cutaneous lesions only?	C1
CQ23: Is interferon therapy recommended for ATLL with cutaneous lesions only?	C1
CQ24: Is single-agent chemotherapy recommended for ATLL with cutaneous lesions only?	B-C1

Eruptions specific to ATLL are defined as cutaneous symptoms in cases seropositive for anti-HTLV-1 antibody and where cutaneous histology shows monoclonal integration of HTLV-1. In the present guidelines, we have provisionally considered "ATLL with cutaneous lesions only" to be "cases in which ATLL cells account for <5% of all peripheral blood cells, excluding the acute, lymphoma, and chronic types".[19,40]

CQ20: Is UV light therapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: B-C1.
Recommendation: PUVA therapy can induce remission in ATLL with cutaneous lesions only, and may be useful. Regardless of whether extracutaneous lesions are present, PUVA can be expected to relieve cutaneous symptoms. However, beneficial effects of PUVA on extracutaneous lesions or the prognosis of patients have not been confirmed (Data S1).

CQ21: Is radiation therapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: B.
Recommendation: Radiation therapy can be expected to provide symptomatic relief in ATLL with cutaneous lesions only, and is recommended. However, beneficial effects on the prognosis of patients have not been confirmed (Data S1).

CQ22: Are oral retinoids recommended for ATLL with cutaneous lesions only?
Degree of recommendation: C1.
Recommendation: Retinoids can induce remission in ATLL with cutaneous lesions only, and may be considered for use (Data S1).

CQ23: Is IFN therapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: C1.
Recommendation: IFN-γ can relieve symptoms in ATLL with cutaneous lesions only, and may be considered for use. Beneficial effects on extracutaneous lesions or the prognosis of patients have not been confirmed (Data S1).

CQ24: Is single-agent chemotherapy recommended for ATLL with cutaneous lesions only?
Degree of recommendation: B-C1.
Recommendation: Single-agent chemotherapy can be useful for disease refractory to skin-direct therapy in cases where combination chemotherapy is not indicated. However, beneficial effects on the prognosis of patients have not been confirmed (Data S1).

Other T/NK-cell lymphomas

In addition to ENKL, the WHO classification for hematopoietic malignancies, revised in 2008, has listed hydroa

vacciniforme-like lymphoma as an independent disease (Table 14).[2] This condition has been reported in Asia, including Japan, in Mexico, and in Peru. Hydroa vacciniforme-like lymphoma is a form of T-cell lymphoma that is associated with EBV. It occurs most frequently in children and adolescents, and is often accompanied by photosensitivity and hypersensitivity to insect bites. Prognosis, although varied, is poor if complicated by systemic conditions such as hemophagocytosis. There have been no reports of treatment for this condition alone, but a few reports are available on treatment of chronic active EBV infection and on EBV^+ T/NK-cell lymphoproliferative diseases. Treatment has been attempted with antiviral therapy using the antiviral agents acyclovir and ganciclovir, immunotherapy using agents such as IFN-α and interleukin 2, and chemotherapy using corticosteroids and etoposide.[44] However, the reports involve a very small number of cases, insufficient even for descriptive research, so findings cannot be considered conclusive.

Blastic plasmacytoid dendritic cell neoplasm is a rare disease formerly designated as $CD4^+/CD56^+$ hematodermic neoplasm.[45] Most patients usually respond to initial polychemotherapy, but the relapse rate is high. The prognosis is dismal, with a median overall survival of 12–14 months.

ENKL, nasal type.

CQ25: Is CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) chemotherapy recommended for ENKL, nasal type?

Degree of recommendation: C2.

Recommendation: ENKL, nasal type, generally responds poorly or only temporarily to CHOP therapy; this treatment is not recommended (Data S1).

CQ26: Is combination radiation therapy and chemotherapy recommended for ENKL, nasal type?

Degree of recommendation: B.

Recommendation: For localized lesions, radiation therapy with simultaneous or subsequent DeVIC (dexamethasone, VP16, ifosfamide, carboplatin) chemotherapy is recommended (Data S1).

Blastic plasmacytoid dendritic cell neoplasm.

CQ27: Is chemotherapy recommended for blastic plasmacytoid dendritic cell neoplasm?

Degree of recommendation: C1.

Recommendation: No standard treatment has been established for blastic plasmacytoid dendritic cell neoplasm. Multidrug chemotherapy may be considered. However, such treatment provides only temporary effectiveness, and almost all patients die within a few years (Data S1).

Hydroa vacciniforme-like lymphoma.

CQ28: Is allogenic hematopoietic stem cell transplantation recommended for hydroa vacciniforme-like lymphoma?

Degree of recommendation: B-C1.

Recommendation: Allogenic hematopoietic stem cell transplantation may be useful in the treatment of hydroa vacciniforme-like lymphoma (Data S1).

Cutaneous B-cell lymphoma

The WHO–EORTC classification of 2005 lists the following subtypes within the category of cutaneous B-cell lymphoma:[1] primary cutaneous marginal zone B-cell lymphoma (PCMZL); primary cutaneous follicle center cell lymphoma (PCFCL), primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, leg type); PCLBCL, other; and intravascular large B-cell lymphoma (IVL) (Table 15). In the 2008 revision of the WHO classification of hematopoietic malignancies, the nomenclature, the PCMZL was replaced by "extranodular marginal zone B-cell lymphoma (MALT lymphoma)".[2] The term, PCDLBCL, leg type, was entered as a subcategory of "diffuse large B-cell lymphoma, not otherwise specified". The term "primary cutaneous diffuse large B-cell lymphoma, other" was removed from the list. Disease type is an important prognostic factor for cutaneous B-cell lymphoma. Both PCFCL and PCMZL are indolent-type lymphomas with a favorable prognosis, while prognosis is poor in PCDLBCL and IVL. In the following discussion, cutaneous B-cell lymphoma is divided into two groups: the indolent group and diffuse large cell group.

No randomized clinical trials have been conducted in these disease groups, and research has been limited primarily to descriptive studies. However, in 2008, the EORTC and ISCL published guidelines for the treatments of cutaneous B-cell lymphoma, based on previous reports.[46] Most of the reported treatment methods for topical therapy involved radiation and/or surgical resection. Most of the methods for systemic therapy involved chemotherapy and the administration of rituximab. However, a few reports were found on topical administration of IFN-α and on the use of photodynamic therapy.

Table 14. Summary of CQ and degree of recommendation for other natural killer (NK)/T-cell lymphomas and related diseases

Clinical question	Degree of recommendation
CQ25: Is CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) chemotherapy recommended for extranodal NK/T-cell lymphoma, nasal type?	C2
CQ26: Is combination radiation therapy and chemotherapy recommended for extranodal NK/T-cell lymphoma, nasal type?	B
CQ27: Is chemotherapy recommended for blastic plasmacytoid dendritic cell neoplasm?	C1
CQ28: Is allogenic stem cell transplantation recommended for hydroa vacciniforme-like lymphoma?	B-C1

Table 15. Summary of CQ and degree of recommendation for primary cutaneous B-cell lymphoma (indolent type: primary cutaneous follicle center lymphoma and extranodal marginal zone lymphoma)

Clinical question	Degree of recommendation
CQ29: Is radiation therapy recommended for indolent-type primary cutaneous B-cell lymphoma?	B
CQ30: Is surgical resection recommended for indolent-type primary cutaneous B-cell lymphoma?	B
CQ31: Is rituximab monotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?	B-C1
CQ32: Is combination chemotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?	C1
CQ33: Is combination chemotherapy recommended for primary cutaneous diffuse large B-cell lymphoma?	B
CQ34: Is rituximab monotherapy recommended for primary cutaneous diffuse large B-cell lymphoma?	B
CQ35: Are surgical resection and radiation therapy recommended for diffuse large B-cell lymphoma?	C1

CQ29: Is radiation therapy recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: B.
Recommendation: Radiotherapy is recommended for diseases in the indolent group (PCMZL and PCFCL) (Data S1).

CQ30: Is surgical resection recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: B.
Recommendation: Surgical resection is recommended for resectable lesions of diseases in the indolent group (PCMZL and PCFCL) (Data S1).

CQ31: Is rituximab monotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: B-C1.
Recommendation: Rituximab may be useful for the treatment of diseases in the indolent group (PCMZL and PCFCL), particularly in cases of multiple lesions (Data S1).

CQ32: Is combination chemotherapy recommended for indolent-type primary cutaneous B-cell lymphoma?
Degree of recommendation: C1.
Recommendation: Combination chemotherapy may be considered for diseases in the indolent group that are refractory to other treatment regimens, and for advanced extracutaneous disease (Data S1).

CQ33: Is combination chemotherapy recommended for PCDLBCL?
Degree of recommendation: B.
Recommendation: Combination chemotherapy, and particularly the concomitant use of rituximab, is recommended for PCDLBCL, leg type, and for IVL (Data S1).

CQ34: Is rituximab monotherapy recommended for PCDLBCL?
Degree of recommendation: B.
Recommendation: Rituximab monotherapy is recommended for the treatment of PCDLBCL in cases where combination therapy may be poorly tolerated, such as in the elderly and in patients with severe complications (Data S1).

CQ35 Are surgical resection and radiation therapy recommended for PCDLBCL?
Degree of recommendation: C1.
Recommendation: In patients who cannot tolerate rituximab combination chemotherapy, such as the elderly and patients with severe complications, surgical resection and radiation therapy may be considered (Data S1).

ACKNOWLEDGMENTS

This work has been made possible by a collaborative project of the Japanese Dermatological Association (JDA), Japanese Skin Cancer Society (JSCS) – Lymphoma Study Group, and Japanese Society of Clinical Oncology – Skin Cancer Guideline Committee, and supported by grants from the Ministry of Health, Labour and Welfare: H21-Clinical Cancer Research-023 (chief researcher, Koichi Hirata), H23-Clinical Cancer Research -021 (chief researcher, Toshiki Watanabe), and H23-Clinical Cancer Research-020 (chief researcher, Kaoru Uchimaru).

REFERENCES

1 Willemze R, Jaffe ES, Burg G *et al.* WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–3785.
2 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press.
3 Olsen E, Vonderheid E, Pimpinelli N *et al.* Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 1713–1722.
4 Kim YH, Willemze R, Pimpinelli N *et al.* TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 479–484.
5 Whittaker SJ, Marsden JR, Spittle M, Russell Jones R. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol* 2003; **149**: 1095–1107.
6 Trautinger F, Knobler R, Willemze R *et al.* EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. *Eur J Cancer* 2006; **42**: 1014–1030.
7 Dummer R. Primary cutaneous lymphomas: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2007; **18**(Suppl 2): ii61–ii62.
8 Iwatsuki K, Kawai K, Ohtsuka M *et al.* Guidelines for the management of cutaneous malignant tumors II: cutaneous lymphomas. *Jpn J Dermatol* 2009; **119**: 1189–1211.

9 Kim EJ, Hess S, Richardson SK *et al.* Immunopathogenesis and therapy of cutaneous T cell lymphoma. *J Clin Invest* 2005; **115**: 789–812.
10 Bunn PA Jr, Huberman MS, Whang-Peng J *et al.* Prospective staging evaluation of patients with cutaneous T-cell lymphomas. Demonstration of a high frequency of extracutaneous dissemination. *Ann Intern Med* 1980; **93**: 223–230.
11 Sausville EA, Eddy JL, Makuch RW *et al.* Histopathologic staging at initial diagnosis of mycosis fungoides and the Sézary syndrome. Definition of three distinctive prognostic groups. *Ann Intern Med* 1988; **109**: 372–382.
12 Olsen EA, Whittaker S, Kim YH *et al.* Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol* 2011; **29**: 2598–2607.
13 Vonderheid EC, Bernengo MG, Burg G *et al.* Update on erythrodermic cutaneous T-cell lymphoma: report of the International Society for Cutaneous Lymphomas. *J Am Acad Dermatol* 2002; **46**: 95–106.
14 Senff NJ, Willemze R. The applicability and prognostic value of the new TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: results and comparison with the system used by the Dutch Cutaneous Lymphoma Group. *Br J Dermatol* 2007; **157**: 1205–1211.
15 Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984–87). *Br J Haematol* 1991; **79**: 428–437.
16 Lister TA, Crowther D, Sutcliffe SB *et al.* Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: cotswolds meeting. *J Clin Oncol* 1989; **7**: 1630–1636.
17 Lymphoma Study Group of Japanese Pathologists. The World Health Organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. *Pathol Int* 2000; **50**: 696–702.
18 Suzuki S, Ito K, Ito M, Kawai K. Prognosis of 100 Japanese patients with mycosis fungoides and Sézary syndrome. *J Dermatol Sci* 2010; **57**: 37–43.
19 Sawada Y, Hino R, Hama K *et al.* Type of skin eruption is an independent prognostic indicator for adult T-cell leukemia/lymphoma. *Blood* 2011; **117**: 3961–3967.
20 Suzuki R, Suzumiya J, Yamaguchi M *et al.* Prognostic factors for mature natural killer (NK) cell neoplasms: aggressive NK cell leukemia and extranodal NK cell lymphoma, nasal type. *Ann Oncol* 2010; **21**: 1032–1040.
21 Suzuki R, Nakamura S, Suzumiya J *et al.* Blastic natural killer cell lymphoma/leukemia (CD56-positive blastic tumor). Prognostication and categorization according to anatomic sites of involvement. *Cancer* 2005; **104**: 1022–1031.
22 Agar NS, Wedgeworth E, Crichton S *et al.* Survival outcomes and prognostic factors in mycosis fungoides/Sézary sundrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol* 2010; **28**: 4730–4739.
23 Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. *Arch Dermatol* 2009; **145**: 1399–1404.
24 Willemze R, Jansen PM, Cerroni L *et al.* Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood* 2008; **111**: 838–845.
25 Zinzani PL, Quaglino P, Pimpinelli N *et al.* Prognostic factors in primary cutaneous B-cell lymphoma:the Italian study group for cutaneous lymphoma. *J Clin Oncol* 2006; **24**: 1376–1382.
26 Sneff NJ, Hoefnagel JJ, Jansen PM *et al.* Reclassification of 300 primary cutaneous B-cell lymphoma according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. *J Clin Oncol* 2007; **25**: 1581–1587.
27 Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome. *Arch Dermatol* 2003; **139**: 857–866.
28 Bekkenk MW, Jansen PM, Meijer CJ, Willemze R. CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. *Ann Oncol* 2004; **15**: 1097–1108.
29 Stadler R, Otte HG, Luger T *et al.* Prospective randomized multicenter clinical trial on the use of interferonα 2a plus acitretin versus interferonα-2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. *Blood* 1998; **92**: 3578–3581.
30 Stadler R, Kremer A, Luger T, Sterry W. Prospective, randomized, multicentre clinical trial on the use of interferon a 2a plus PUVA versus PUVA monotehrapy in patients with cutaneous T-cell lymphoma, stage I and II. *J Clin Oncol*, 2006 ASCO Annual Meeting Proceedings, 2006; **24**: 7541.
31 Kaye FJ, Bunn PA Jr, Steinberg SM *et al.* A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. *N Engl J Med* 1989; **321**: 1784–1790.
32 Child FJ, Mitchell TJ, Whittaker SJ, Scarisbrick JJ, Seed PT, Russell-Jones R. A randomized cross-over study to compare PUVA and extracorporeal photopheresis in the treatment of plaque stage (T2) mycosis fungoides. *Clin Exp Dermatol* 2004; **29**: 231–236.
33 Prince HM, Duvic M, Martin A *et al.* Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. *J Clin Oncol* 2010; **28**: 1870–1877.
34 Toro JR, Beaty M, Sorbara L *et al.* Gamma delta T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. *Arch Dermatol* 2000; **136**: 1024–1032.
35 Santucci M, Pimpinelli N, Massi D *et al.* Cytotoxic/natural killer cell cutaneous lymphomas. Report of EORTC Cutaneous Lymphoma Task Force Workshop. *Cancer* 2003; **97**: 610–627.
36 Lu D, Patel KA, Duvic M, Jones D. Clinical and pathological spectrum of CD8-positive cutaneous T-cell lymphomas. *J Cutan Pathol* 2002; **29**: 465–472.
37 Toro JR, Liewehr DJ, Pabby N *et al.* Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. *Blood* 2003; **101**: 3407–3412.
38 Bekkenk MW, Vermeer MH, Jansen PM *et al.* Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. *Blood* 2003; **102**: 2213–2219.
39 Berti E, Tomasini D, Vermeer MH, Alessi E, Willemze R. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. *Am J Pathol* 1999; **155**: 483–492.
40 Setoyama M, Katahira Y, Kanzaki T. Clinicopathologic analysis of 124 cases of adult T-cell leukemia/lymphoma with cutaneous manifestations: the smouldering type with skin manifestations has a poorer prognosis than previously thought. *J Dermatol* 1999; **26**: 785–790.
41 Takahashi K, Tanaka T, Fujita M *et al.* Cutaneous-type adult T-cell leukemia/lymphoma. A unique clinical feature with monoclonal T-cell proliferation detected by Southern blot analysis. *Arch Dermatol* 1988; **124**: 399–404.
42 Johno M, Ohishi M, Kojo Y, Yamamoto S, Ono T. Cutaneous manifestations of adult T-cell leukemia/lymphoma. *Gann Monogr Cancer Res* 1992; **39**: 33–42.
43 Amano M, Kurokawa M, Ogata K *et al.* New entity, definition and diagnostic criteria of cutaneous adult T-cell leukemia/lymphoma: human T-lymphotropic virus type 1 proviral DNA load can distinguish between cutaneous and smoldering types. *J Dermatol* 2008; **35**: 270–275.
44 Cohen JI, Kimura H, Nakamura S, Ko YH, Jaffe ES. Epstein–Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8–9 September 2008. *Ann Oncol* 2009; **20**: 1472–1482.

45 Herling M, Jones D. CD4+/CD56+ hematodermic tumor: the features of an evolving entity and its relationship to dendritic cells. *Am J Clin Pathol* 2007; **127**: 687–700.
46 Sneff NJ, Noordijk EM, Kim YH *et al.* European Organization for Research and Treatment of Cancer and International. Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008; **112**: 1600–1609.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. References used for treatment recommendations (CQ1–CQ35).

Table S1. Terminology for clinical features of mycosis fungoides/Sézary syndrome.

Table S2. Tumor, lymph nodes, metastasis, blood (TNMB) classification for mycosis fungoides/Sézary syndrome.

Table S3. TNMB staging for mycosis fungoides/Sézary syndrome (International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer, Cutaneous Lymphomas Task Force).

Table S4. Tumor–node–metastasis classification for primary cutaneous lymphomas other than mycosis fungoides/Sézary syndrome.

Table S5. Ann Arbor/Cotswold staging.

Figure S1. Clinicopathological features of mycosis fungoides/Sézary syndrome.

Figure S2. Clinical features of anaplastic large cell lymphoma.

Figure S3. Clinical features of adult T-cell leukemia/lymphoma.

Figure S4. Clinicopathological features of subcutaneous panniculitis-like T-cell lymphoma.

Figure S5. Clinical features of extranodal natural killer/T-cell lymphoma, nasal type.

Figure S6. Clinicopathological features of hydroa vacciniforme-like lymphoma.

Figure S7. Clinical features of blastic plasmacytoid dendritic cell neoplasm.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

特集 産婦人科性感染症とその対策

HTLV-I 母子感染対策

齋藤 滋*

HTLV-I は，ATL や HAM の原因ウイルスであるが，いったん感染すると薬剤などでウイルスを排除できない。そのため，感染予防が極めて重要であり，母乳を介した母子感染を減少させるため，妊婦にスクリーニングが行われている。一次スクリーニングで陽性となれば，必ずウェスタンブロット(WB)法を確認検査として行い，陽性となればキャリアと同定し，陰性であれば母乳哺育を勧める。判定保留者には，PCR 法を行うことを提案する。キャリアに対して，人工乳，3カ月までの短期母乳，凍結母乳の3つの方法を提示し，それぞれのメリット，デメリットを説明し，患者に選択してもらう。短期母乳，凍結母乳を選択した場合，継続的な地域の助産師，保健師のサポートが必要である。

はじめに

1981年に HTLV-I が ATL(adult T cell leukemia：成人T細胞白血病)の原因ウイルスとして同定され[1]，1991年に重松班より HTLV-I 母子感染に対する見解が発表され[2]，① 全国でキャリアは120万人いる，② 母子感染率は15～25%に生じる，③ 母子感染の主体は母乳を介する経路(母子感染の約90%)である，④ 新しい差別の対象とならないため，キャリア率の高い地域以外では対策不要，と報告された。しかし，2007年の厚生労働研究 山口班報告[3]で，献血者からの HTLV-I キャリア数を推定すると，① 全国で108万人いること，② HTLV-I キャリアが全国に拡散し，もはや九州，沖縄だけのウイルスでなくなったこと，が明らかとなった。HTLV-I 感染は，① 母乳を介した母子感染，② 性行為を介した感染，③ 輸血を介した感染，の3つがあるが，現在は輸血を介した感染は皆無である。ATL の発症は母乳を介した感染のみで生じること，HTLV-I キャリアの減少と ATL，HAM(HTLV-I 関連脊髄症)撲滅のためには，母子感染対策が最も効果的であることから，国は，公費で妊婦に対する HTLV-I 抗体検査を助成するようになった。このことは，HTLV-I の撲滅のためには，極めて有益であるが，突然，キャリアと判明した妊婦に対して，正しい情報を提供することが必要であるのみならず，精神的なケアやフォローアップの対応，退院後の母乳管理を含めた助産師や保健師のサポートが必要になる。これまでは任意の検査であったため，検査のメリットのみが強調されてきたが，これからはデメリットに対する十分な対応が求められる。

1．妊婦スクリーニング方法の実際

図1に示すように，妊娠30週までに抗体検査を行う[4]。大多数は陰性だが，一部の妊婦が陽性者となる。この際，一次抗体スクリーニングには偽陽性のあることを認識すべきであ

* Shigeru Saito 富山大学大学院医学薬学研究部産科婦人科