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REVIEW ARTICLE

T-cell lymphomas, a challenging disease: types, treatments, and future

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Abstract T-cell lymphomas are rare and aggressive malignancies associated with poor outcome, often because of the development of resistance in the lymphoma against chemotherapy as well as intolerance in patients to the established and toxic chemotherapy regimens. In this review article, we discuss the epidemiology, pathophysiology, current standard of care, and future treatments of common types of T-cell lymphomas, including adult T-cell leukemia/lymphoma, angioimmunoblastic T-cell lymphoma, anaplastic large-cell lymphoma, aggressive NK/T-cell lymphoma, and cutaneous T-cell lymphoma.

Keywords Adult T-cell leukemia/lymphoma · Angioimmunoblastic T-cell lymphoma · Anaplastic large cell lymphoma · NK/T-cell lymphoma · Cutaneous T-cell lymphoma · Novel agents

Adult T-cell leukemia/lymphoma (ATLL)

Incidence

Adult T-cell leukemia (ATLL) was first described in Japan by Uchiyama in 1977 with lymphadenopathy, splenomegaly, and bone marrow (BM) infiltration in 16 adults, which was differentiated from cutaneous T-cell lymphoma [1]. The association of ATLL and human T-cell lymphotropic virus (HTLV)-1 virus was discovered because all patients have antibodies against the virus, which corresponded with a high incidence of ATLL patients in areas with a high incidence of HTLV-1 carriers. It was found that HTLV-1 immortalizes human T-cells in vitro, which led to the discovery of monoclonal integration of HTLV-1 proviral DNA in leukemia cells, thus making it the first retrovirus directly associated with human malignancy [2]. The incidence of ATLL is estimated to be 2.5 % among HTLV-1 carriers in endemic areas [3] and, according to SEER data, 0.04 % in the USA, a nonendemic area [4]. ATLL patients constitute 9.6 % of total T-cell lymphomas, 2 % in North America, 1 % in Europe, and 25 % in Asia [5]. In an observational study, men were slightly more likely to be affected, with a sex ratio of male:female = 1.2–1.35:1 and mean age of 57.1 years (range, 24–92 years) [6, 7]. The virus is transmitted by blood transfusion, sharing of needles, sexual intercourse, and breastfeeding. Infections with HTLV-1 and cases of ATLL are endemic in several regions of the world, including southwestern Japan (Kyushu), the Caribbean basin, and Central Africa. A recent epidemiological study revealed that although incidences in endemic areas are stable with annual 0 % increase [95 % confidence interval (CI), −1.6 to 1.7], there is an increase in nonendemic areas in Japan of +4.6 % (CI, 1.1–8.2) as well as in the USA, +6.2 % (CI, 1.5–11.1), with a stable male predominance of 1.26 [8].

Pathophysiology

In the setting of HTLV-1 infection, molecular analyses have found that Tax is a viral regulatory protein associated with malignant transformation because of its function in activating nuclear factor-kappa B (NF-κB), and T-cell trafficking in addition to disrupting immunosurveillance [9].

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NF-κB and Akt pathways are two major cellular pro-survival routes activated by Tax, which initiates the malignant transformation, considering that more than 80 % exhibit DNA aneuploidy. The HTLV-1 basic leucine zipper factor (HBZ) is seen in all ATLL cases [3]. The HBZ protein has a role in promoting viral replication and cellular proliferation, maintaining the malignancy when Tax expression has been extinguished [10]. Regarding phenotype, ATLL cells express T-cell-associated antigens (CD2, CD3, CD5) and mostly CD4$^+$ CD8$^-$, CD25, as well as gain-of-function CCR4 mutations [11] and FoxP3, the master protein of the regulatory T cell [3, 6]. Gains of 7p and 7q and loss of 9p21.3 in addition to mutations of RHOA show a significant association with poor prognosis [12].

Types and classification

Diagnostic criteria and classification of clinical subtypes were first described in 1991 with reports of progression from chronic to acute, which are listed below and in Table 1 [6].

Diagnosis:

1. Histological and cytological malignancy with CD2$^+$, CD3$^+$, and CD4$^+$.
2. Abnormal T lymphocytes in peripheral blood (PB) except for lymphoma type.
3. Presence of antibody to HTLV-1.

Available treatments

It was observed by Shimoyama, from 1984 to 1987, that of 122 patients who did not undergo treatment, 26 (55 %) died within 1 month because of deterioration from the disease and 17 (36 %) died of acute crisis after 3 months from diagnosis. Of the 635 patients who did undergo treatment, 119 (19 %) achieved complete response [6]. Many studies reveal that antiviral and chemotherapy together yield better survival. Major prognostic factors were advanced performance status, high lactic dehydrogenase (LDH) level, age 40 years or older, hypercalcemia caused by increased osteoclasts and accelerated bone resorption, and more extensive involvement [13–15]. Here, we focus on the treatment of the ATLL lymphoma subtype [16].

EPOCH or HyperCVAD

EPOCH or HyperCVAD with high-dose methotrexate and cytarabine are considered to be first-line treatments according to National Comprehensive Cancer Network (NCCN) guidelines. The AIDS malignancy consortium evaluated EPOCH therapy for ATLL [17]. EPOCH therapy was administered as etoposide, vincristine, and doxorubicin, cyclophosphamide, and prednisone. Chemotherapy was administered on a cycle of 21–28 days for a minimum of two cycles beyond best response and a maximum of six cycles. Prophylaxis for pneumocystis pneumonia and tumor lysis syndrome was provided. Central nervous system prophylaxis was either cytosine arabinoside or intrathecal methotrexate. One month after the last cycle of chemotherapy, antiretroviral therapy was initiated, including zidovudine plus lamivudine and interferon-alpha-2a daily for 1 year. Eleven of a total of 19 patients had responsive disease, including two complete remissions and nine partial remissions, for an overall response rate (ORR) of 91 % for evaluable patients (95 % CI, 0.6–0.99) and 58 % for all patients (95 % CI, 0.36–0.77). Disease relapse occurred in 4 patients. Nine patients remained alive at time of data presentation and 16 months after completion of therapy. Although the disease is caused by HTLV-1, treatment of the virus does not necessarily lead to cure.

VCAP/AMP/VECP

The current chemotherapy approach for newly diagnosed lymphomatous ATLL as proposed by the International

Table 1 Adult T-cell leukemia/lymphoma (ATLL): classifications and characteristics

Type, n (%)	Smoldering, 45 (5.5)	Chronic, 152 (18.6)	Lymphoma, 156 (19.1)	Acute, 465 (56.8)
Abnormal T cells	>5 % in PB, normal lymphocyte level	>5 % in PB, lymphocytosis	<1 % in PB, no lymphocytosis	Both leukemia and tumor
Labs	No hypercalcemia, LDH >1.5× nl	No hyperCa, LDH >2× nl	Some hyperCa, LDH >2× nl	50 % hyperCa, LDH >3× nl
LAD	None	Present	Present	Present
Organs involved	Rare, skin and lungs	Liver, spleen, skin, lung	+/−	Present
MST	Not reached at end of study	24.3 months	10.2 months	6.2 months
Two-year survival	77.7 %	52.4 %	21.3 %	16.7 %
Four-year survival	62.8 %	26.9 %	5.7 %	5 %

Consensus Meeting in 2009 uses VCAP–AMP–VECP, although this treatment is not available in the United States. The treatment consists of vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP), doxorubicin, ranimustine, and prednisone (AMP), and vindesine, etoposide, carboplatin, and prednisone (VECP). This regimen was tested solely in Japan because ranimustine is a nitrosurea alkylating agent (MCNU) that is only available there. This regimen was initially studied in a phase II trial with granulocyte colony-stimulating factor (G-CSF) support in the LSG15 protocol. Therapy consisted of seven cycles of VCAP–AMP–VECP. Eighty-one per cent of the 93 eligible patients responded (95 % CI, 0.71–0.88), with 33 patients obtaining complete response (CR) (35.5 %) and 42 obtaining partial response (PR) (45.2 %). The median survival time (MST) after registration was 13 months, and the median follow-up duration of the 20 surviving patients was 4.2 years (range, 2.8–5.6 years). Overall survival (OS) at 2 years was estimated to be 31.3 % (95 % CI, 0.22–0.405) [18]. In a phase III clinical trial, VCAP–AMP–VECP was compared to biweekly CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with a total of 118 patients enrolled [19]. Both arms used intrathecal methotrexate for prophylaxis because of the high frequency of central nervous system (CNS) relapse. Median follow-up time for all randomly assigned patients was 10.9 months. The complete response (CR) rate was higher in the VCAP–AMP–VECP arm than in the biweekly CHOP arm (40 % vs. 25 %, respectively; $p < 0.02$). Progression-free survival (PFS) rate at 1 year was 28 % in the VCAP–AMP–VECP arm compared with 16 % in the CHOP arm ($p < 0.1$; two-sided $p < 0.2$). OS at 3 years was 24 % in the VCAP–AMP–VECP arm and 13 % in the CHOP arm ($p < 0.085$; two-sided $p < 0.169$). This study highlighted that CHOP chemotherapy is not sufficient as treatment for ATLL and that we should consider a more cytotoxic regimen.

Arsenic/interferon-alpha/zidovudine

A phase II study of intravenous arsenic trioxide, subcutaneous interferon-alpha, and oral zidovudine was done to analyze response in patients with ATLL [20]. At day 30, five patients had achieved partial response (PR) and five had achieved very good partial response (VGPR), defined as normalization of the complete blood count (CBC), but with persistence of more than 5 % of atypical lymphocytes on peripheral blood smear. Skin lesions improved and viral load significantly decreased from an average of 1415 copies/μl to 226 copies/μl ($p < 0.05$). All patients were alive without relapse or disease progression at the 8-month follow-up. ATLL patients in a follow-up study were found to have increased Treg and Th2 transcription of elevated Foxp3, interleukin (IL)10, and IL4, with reduced Th1 in a setting of decreased interferon (IFN)-gamma and IL2

compared to healthy HTLV-1 carriers. After treatment with arsenic/IFN/zidovudine, repeat analysis revealed trends toward normalization [21].

A review of AZT and interferon-alpha in 207 patients with ATLL with data for 124 patients, with 62 on antiviral therapy, showed that 35 % of patients achieve CR, 31 % PR, and 34 % no response at 1 month. Of 48 patients on chemotherapy, only 25 % achieved CR, 56 % PR, and 19 % no response. Of 14 patients who received chemotherapy and then antiviral therapy, 50 % achieved CR, 43 % PR, and 7 % no response. Overall median survival was 12 months, and 5-year OS was 23 %. The chronic/smoldering type had the best prognosis as patients had not reached death for median death analysis and had 76 % 5-year survival compared to acute type with a survival of 6 months and 15 % of the patients versus ATLL lymphoma type survival of 13 months and 16 % of patients. In lymphoma ATLL type, the antiviral therapy-only group ($n = 13$) had a survival disadvantage with 7 months median survival and 0 % 5-year OS compared with the chemotherapy group ($n = 71$) with or without maintenance antiviral therapy, which resulted in 16-month median survival and 18 % 5-year OS ($p = 0.009$) [22]. Again, treating the virus did not correlate with improved survival.

Allogeneic stem cell transplant (allo-HSCT)

Allogeneic stem cell transplant is important for patients to reach CR, and that is the standard of care internationally. Allo-HSCT was studied for acute and lymphoma types of ATLL in seven institutions in Japan between 1997 and 2002. All evaluable cases entered CR after allo-HSCT, and the median survival time was 9.6 months for all patients. The estimated 3-year overall and relapse-free survival, and disease relapse, were 45.3 %, 33.8 %, and 39.3 %, respectively [23]. Conditioning with myeloablative conditioning regimen (MAC) is varied, and in one study, ten patients received total body irradiation (10–13.2 Gy) along with some combination of cyclophosphamide (CY), melphalan, cytosine-arabinoside (CA), and etoposide (ETO), in addition to granulocyte colony-stimulating factor. Side effects included nausea, vomiting, stomatitis, as well as hemorrhagic cystitis, CMV antigenemia, zoster, pneumonitis, and septicemia. The median leukemia-free survival after allo-HSCT was 17.5 months (range, 3.7–34.4 months) and five patients were disease free at a median of 31.5 months. Two (20 %) patients relapsed at 3.7 and 4.0 months after allo-SCT, and four (40 %) patients died. The causes of death included renal insufficiency after relapse, interstitial pneumonitis, gastrointestinal bleeding probably caused by thrombotic microangiopathy, and grade IV acute graft-versus-host disease (GVHD) [24]. Given the high mortality of the myeloablative conditioning regimen in the elderly,

reduced intensity conditioning (RIC) using peripheral blood of HLA-matched siblings after undergoing a conditioning regimen consisting of fludarabine, busulfan, and rabbit antithymocyte globulin for patients aged 50–70 years has been found to be effective [25]. A Japanese nationwide retrospective study found that in transplant recipients, median OS and 3-year OS of bone marrow or peripheral blood transplantation recipients ($n = 586$) was 9.9 months (95 % CI, 7.4–13.2 months) and 36 % (32–41 %), respectively. Median OS and 3-year OS for recipients of myeloablative conditioning for those younger than 55 years were 9.5 months (6.7–18.0 months) and 39 % (33–45 %), and RIC for patients 50–70 years of age was 10.0 months (7.2–14.0 months) and 34 % (29–40 %), respectively. Multivariate analysis demonstrated five significant variables contributing to poorer OS, namely, older age, male sex, not in complete remission, poor performance status, and transplantation from unrelated donors. Although no significant difference in OS between MAC and RIC was observed, there was a trend indicating that RIC contributed to better OS in older patients [26].

A comparison was made with the 1991 database with information from 2000 to 2009. Looking at the lymphoma type, mean age was 59.2 years in 1991 and 66 years in the 2000s. Mean survival was 10.2 months in 1991 and 10.6 months in the 2000s, but without allo-HSCT it was 9.7 months compared to 13.9 months with transplant. Four-year overall survival (OS) improved from 5.7 % to 16.2 %; it was 13.7 % without allo-HSCT and 32.3 % with transplant. Although this is a very difficult disease to treat, innovations in management seem to have improved survival [27]. In a retrospective study, early stem cell transplant patients may have a better chance of OS. The patients were grouped in either the early allo-HSCT group within 100 days of diagnosis ($n = 72$) or the late transplant group at 100 days or more ($n = 428$), and the median age of patients enrolled was 52 years. The corresponding constituents of disease status were not statistically different between the two groups ($p = 0.11$). The probability of OS in the early transplant group was significantly higher than in the late transplant group (4-year OS, 49.3 % vs. 31.2 %). Multivariate analysis revealed that late allo-HSCT was an unfavorable prognostic factor for OS (HR, 1.46, 95 % CI, 1.01–2.11; $p = 0.04$) [28]. Another retrospective study in Japan examined the impact on GVHD on survival in patients with ATLL. Patients with lymphoma type were found to have worse outcomes. In grade I–II acute GVHD, the hazard ratio (HR) was found to be 1.82 (95 % CI, 1.03–3.24) compared to chronic/smoldering with HR of 0.24 (95 % CI, 0.05–1.03) and acute with HR of 0.5 (95 % CI, 0.34–0.73). In grade III–IV acute GVHD, the HR for lymphoma type was 2.11 (95 % CI, 0.97–4.53) compared to chronic/smoldering with HR of 0.75 (95 % CI, 0.14–3.98)

and acute with HR of 1.42 (95 % CI, 0.9–2.23). Chronic GVHD seemed to have protective effects on ATLL-related mortality compared to not having GVHD, but the opposite is true when looking at treatment-related mortality [29].

To understand viral activity after allogeneic hematopoietic stem cell transplant for treatment of ATLL, a study found that most of the 22 patients sampled who underwent transplant still contain a low amount of HTLV-1 provirus. Only 1 patient was found to have no HLTV-1 genome amplified in polymerase chain reaction (PCR) tests or antibodies, suggesting viral clearance, but it appeared that ATLL disease control could be obtained without complete elimination of the causative virus [30].

Future novel treatments

Mogamulizumab (KW-0761, Poteligeo)

CCR4 is a chemokine receptor that has an important role in immune cell trafficking, expressed on T-helper type 2 cells (Th2), regulatory T cells (T_{reg}), interleukin-17-producing T-helper cells (Th17), and skin-homing memory T cells. The leukemic cells in 90 % of ATLL cases express CCR4 on their surface [31]. Mogamulizumab, which is an anti-CCR4 monoclonal antibody, has been studied in ATLL patients with CCR4 disease. Of the 28 patients with relapsed ATLL studied, 27 received at least one infusion of mogamulizumab weekly for 8 weeks. Objective responses were noted in 13 of 26 evaluable patients, including eight complete responses, with an overall response rate of 50 % (95 % CI, 0.30–0.70) [32]. Median progression-free and overall survivals were 5.2 and 13.7 months, respectively. The most common adverse events were infusion reactions (89 %) and skin rashes (63 %), which were manageable and reversible. Treatment with mogamulizumab before allogeneic hematopoietic stem cell transplantation in treatment of ATLL has been documented to induce severe acute graft-versus-host disease (GVHD) in 64 % (95 % CI, 40.7–80.1 %) for grade II–IV with cumulative incidence of transplantation-related mortality of 49 % (95 % CI, 27–67.8 %), especially with less than 3 months between treatments [33].

Ishida et al. enrolled 54 patients to compare a modified version of the Japanese standard of care (mLSG15) with and without mogamulizumab [34]. The mLSG15 protocol consists of three chemotherapeutic regimens, namely, VCAP, AMP, and VECP. Subjects assigned to the mLSG15-plus-mogamulizumab arm received up to eight infusions of mogamulizumab during four cycles of mLSG15. Cytarabine, methotrexate, and prednisolone were intrathecally injected before initiation of VCAP administration in cycles 2 and 4. Of the 29 and 24 patients evaluable for efficacy in the mLSG15-plus-mogamulizumab and the mLSG15

arms, 25 patients (ORR, 86 %; 95 % CI, 0.68–0.96) and 18 patients (ORR, 75 %; 95 % CI, 0.53–0.9), respectively, had objective responses. The percentage of CR was higher in the mLSG15-plus-mogamulizumab arm (52 %; 95 % CI, 0.33–0.71) than in the mLSG15 arm (33 %; 95 % CI, 0.16–0.55), with a between-group difference of 18.4 % (95 % CI, 0.09–0.44). Side effects include skin disorders, cytomegalovirus infection, pyrexia, hyperglycemia, and interstitial lung disease, which were more frequent in the arm with mogamulizumab. Results of this study suggest adding mogamulizumab to the standard of care has a better response but with increased risk of side effects.

PJ-34

PJ-34 is a small molecule inhibitor of poly (ADP-ribose) polymerase (PARP) that can induce apoptosis, particularly in ATLL. Because PJ-34 has been tested in clinical trials for the treatment of solid tumors, results suggest that some ATLL patients may benefit from PJ-34 therapy, but HTLV-1-transformed MT2 cells are found to be resistant to therapy [35]. This small molecule is currently under study and alteration, and it is something to look for in the future for its possible role in the treatment of ATLL.

Angioimmunoblastic T-cell lymphoma (AITL)

Incidence

Angioimmunoblastic T-cell lymphoma (AITL), also known as angioimmunoblastic lymphadenopathy dysproteinemia T-cell NHL (AILD), was first described in 1974 as an aggressive disease of the elderly, characterized by acute onset of constitutional symptoms, lymphadenopathy, hepatosplenomegaly, and dysgammaglobulinemia with immune compromise appearing similar to graft-versus-host disease [36]. There are also reports of varied skin findings in 50 % of patients [37–39]. It is a subtype of peripheral T-cell lymphoma that represents 18.5 % of cases with 16 % in North America, 34.3 % in Europe, and 22.4 % in Asia [5]. Interestingly, a recent French study found that AITL (739 cases, 36 %) is the most frequent peripheral T-cell lymphoma in France by using Lymphopath, the national lymphoma network [40]. Prognosis is poor, with 5-year overall survival ranging between 35 % and 48 % and 5-year progression-free survival (PFS) around 25 % [41, 42].

Pathophysiology

Angioimmunoblastic T-cell lymphoma has not been associated with a particular causal etiology. Studies have found no exposure or geographic predisposition but that there could be an association with immunocompromised status, infections, or antibiotic use [43–45] as well as with autoimmune thrombocytopenia [46]. Among many microorganisms, Epstein–Barr virus (EBV) and HHV-6 in particular are detectable in the great majority of tumors, likely caused by the immunocompromised status in AITL patients [47–52]. EBV co-infection may lead to B-cell malignancy with primary T-cell malignancy, although EBV involvement in the pathogenesis of the disease is still debated. Cytogenetic abnormalities including trisomy 3 and trisomy 5 with T-cell receptor (TCR) rearrangement were found in up to 85–90 % of cases [53]. RHOA, TET2, IDH2, and DNMT3A mutations have been found to be associated with the disease pathogenesis [54–62]. Gene expression analyses of AITL in mouse studies showed that essentially all cases expressed elevated levels of transcripts for IL21, IL21R, and a series of genes associated with follicular helper T-cell (TFH) development and function [63]. Expression of CD3, CD10, CD28, CD30, CXCL13, ICOS, and PD1 has been detected with histopathological staining of AITL cells [43, 54, 64–73]. Because of the compatible expression of CD3, CD4, CD10, and CXCL13, AITL is thought to be the overproliferation of germinal center T-helper cells with CXCL13, which is important in B-cell recruitment and activation, likely contributing to B-cell abnormalities also seen in patients [74, 75]. Recently, an analysis of microRNA suggests upregulation of miR-146a, miR-193b, and miR-34a, which may contribute to the oncogenesis of AITL [76].

Types and classification

AITL is a systemic disease characterized by a polymorphous infiltrate involving lymph nodes, with pathology revealing prominent high endothelial venules (HEV) and perivascular expansion of follicular dendritic cell (FDC) meshworks [77]. The cases of AITL are categorized into pattern I, pattern II, and pattern III according to the presence of hyperplastic follicles, regressed follicles, or absence of identifiable follicles [64]. Pattern I, which constitutes 18.75 % of AITL, was noted to have partial preservation of the lymph node architecture with hyperplastic B-cell follicles with poorly developed mantle zones and poorly defined borders identifiable in the cortex of the lymph node. Pattern II, 32.25 % of AITL, was characterized by loss of normal architecture except for an occasional depleted follicle with concentrically arranged FDCs. In pattern III, 43.75 % of AITL, the normal architecture was completely effaced and no B-cell follicles could be identified; prominent irregular proliferations of FDCs with extensive vascular proliferation were noted. All three groups had a polymorphic infiltrate of lymphocytes and transformed large lymphoid blasts, plasma cells, macrophages, and

eosinophils. Diffuse effacement and neovascular infiltration by plasma cells and immunoblasts are seen [53].

Available treatments

Factors associated with worse prognosis were male sex, poorer performance status, and high prognosis index score, higher WBC count, anemia, lower albumin, extranodal involvement, and mediastinal lymphadenopathy [41, 78]. Another study found AITL, which is usually a disease of the elderly, with multifactorial etiologies of immunocompromise, standard chemotherapy, and stem cell transplant, to be associated with higher morbidity and mortality; overall 5-year survival was about 30 % [73]. One review found AILD patients as the subgroup with the worst prognosis of all T-cell lymphomas, with only one of seven patients surviving longer than 3 years [79]. According to the NCCN, treatment is grouped with other subtypes under peripheral T-cell lymphomas, but results are not favorable, and clinical trials are preferred as first-line therapy. If patients can tolerate further treatment, they should undergo consolidation with high-dose therapy and stem cell rescue to try and achieve complete remission.

CHOP, CHOEP, COEP-B

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone), and COEP-B (cyclophosphamide, vincristine, epirubicin, prednisone, bleomycin) have been studied in AITL patients.

CHOP has been studied for six cycles in 33 patients with angioimmunoblastic lymphadenopathy T-cell lymphoma (AILD). Patients enrolled in the study had a median age of 52 years [80]. Twenty of the 33 patients (61 %) achieved CR, with progression-free response ranging from 3 to 108 months with a median of 26 months, and 9 patients with persistent first CR; 5-year OS was 36.2 %. Adverse events leading to death included immune suppression resulting in severe infection as well as acute respiratory distress syndrome (ARDS). More recently, CHOP-21 and CHOEP-21 were cycled every 3 weeks, and CHOP-14 and CHOEP-14 were cycled every 2 weeks, in patients with T-cell lymphoma, supported by recombinant human G-CSF (filgrastim) from days 4 to 13. Few patients enrolled had AITL, and the complete remission rates for the whole study were 60.1 % (CHOP-21), 70.0 % (CHOEP-21), 76.1 % (CHOP-14), and 71.6 % (CHOEP-14). Five-year event-free and OS rates were 32.5 % and 40.6 %, respectively, for CHOP-21 and 43.8 % and 53.3 %, respectively, for CHOP-14. In a multivariate analysis, the relative risk reduction was 0.66 ($p = 0.003$) for event-free and 0.58 ($p < 0.001$) for OS after CHOP-14 compared with CHOP-21. Because

of its favorable efficacy and toxicity profile, CHOP-14 was recommended for patients ages 60 or older with aggressive T-cell lymphoma [81, 82]. A follow-up study comparing CHOEP 14 and 21 for aggressive T-cell lymphoma patients, although only 1 of 139 AITL patients received CHOEP-14, found that with CHOEP-21, 63 of 78 (80.8 %) patients achieved CR and 7.7 % PR whereas 9.0 % had progressive disease under treatment. Of the patients who received CHOEP-14, 27 of 41 (65.8 %) achieved CR and 12.2 % PR, with 17.1 % having progression under therapy. Four-year event-free survival (EFS) was 47.9 % after CHOEP-14 and 66.2 % after CHOEP-21, and 4-year OS was 62.1 % after CHOEP-14 and 73.4 % after CHOEP-21, respectively, suggesting a longer cycle may have better outcomes in patients younger than 60 [82, 83]. Studies conducted by the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) found that for patients with AITL (27 % of patients studied) receiving six to eight courses of CHOP or CHOEP to have a 3-year EFS of 50.0 % (95 % CI, 31.6–68.4 %) with OS of 67.5 % (95 % CI, 50.1–84.9 %) [84]. Treatment for 28 days was found to have a CR rate of 70 %; however, many patients relapsed, with 5-year OS of 36 % [42]. Accordingly, upfront hematological stem cell transplant in patients with AITL after achieving CR should be considered to prevent relapse. COEP-B with or without radiotherapy was studied in 52 patients with median age of 47 years (range, 17–78 years). Five (10 %) of patients had AITL [85]; 2 (40 %) had a complete response and 2 (40 %) had a partial response. Toxicities included nausea, vomiting, neutropenia, and thrombocytopenia, as well as deadly adverse events of pancreatitis and intracranial hemorrhage.

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)

DA-EPOCH cycles are given every 21 days, and studies have shown efficacy in AITL. One study showed that in 74 assessable patients with relapsed or refractory non-Hodgkins lymphoma (diffuse large-cell and large-cell immunoblastic were the predominant histologies, comprising 61 %) had an overall response rate of 87 % (95 % CI, 77–94 %), which included 27 % CRs (95 % CI, 17–39 %) and 60 % PRs (95 % CI, 48–72 %). A median of 4.5 cycles was administered, with best response seen at a median of 4 cycles. The best response was seen in low-grade lymphomas [86].

Induction therapy followed by conditioning chemotherapy and auto-HSCT

Twenty-nine patients with angioimmunoblastic T-cell lymphoma, at an average 51 years of age with international prognostic factor index (IPI) of 79 %, were studied after using

high-dose chemotherapy (HDCT) regimens before conditioning chemotherapy and HSCT [87]. Of those conditioning chemotherapies analyzed, 7 of 39 (24 %) of patients underwent ICE or ICE-like therapy followed by hematopoietic stem cell transplant with growth factors. Patients who received HDCT and HSCT had a median age of 53 years (range, 20–60 years). The CR rates after transplantation in patients who were treated with HDCT as part of first-line (with CHOP or intensive combination therapies), second-line (salvage with DexaBEAM, CHOP, ESHAP, and other regimens), and third-line therapy with other salvage therapies were 86 %, 70 %, and 60 %, respectively ($p = 0.446$). Of the 5 patients after transplantation (although not differentiated among conditioning therapies), 4 patients achieved remission and 1 of these 4 patients is still alive in continuous CR 4 years later. Of 22 patients who achieved CR after HDCT, 9 patients (41 %) relapsed. The 5-year OS was 62 % (95 % CI, 48–86 %) and event-free survival 49 % (95 % CI, 24–74 %). At last follow-up, 5 patients had been in continuous CR for more than 5 years (range, 6–10 years after HSCT).

After four to six cycles of CHOP, an induction therapy with either the DexaBEAM (dexamethasone, carmustine, melphalan, etoposide, cytarabine) or the ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) protocol was administered. If a CR or a PR was achieved, myeloablative radiochemotherapy (hyperfractionated total-body irradiation and high-dose cyclophosphamide) with autologous peripheral blood stem cell transplant was performed. Thirty patients enrolled, with AITL constituting 12 of 30 (40 %). The main toxicities were myelosuppression and infections. The overall response rate after myeloablative therapy was 100 % (20 CR, one PR). In total, 16 of 21 transplanted patients (76 %) remained in CR at a median follow-up of 15 months (range, 6–32 months) [88]. A follow-up study with CHOP for four to six cycles, then stem cell-mobilizing therapy with DexaBEAM or ESHAP, was followed by myeloablative radiochemotherapy. Twenty-seven of the 83 patients were diagnosed with AITL, and 65 of all patients started stem cell-mobilizing therapy with 39 % CR and 20 % PR after induction therapy [89]. Six patients had early relapse, 2 refused high-dose therapy, 1 died of treatment-related infection, and another died of mesenteric venous thrombosis, limiting them from stem cell therapy (SCT). Fifty-five of the 83 patients underwent autologous SCT with overall response rate (ORR) of 66 % (58 % CR and 8 % PR), but 22 patients experienced relapse. Three-year OS was 48 %; more specifically, 71 % for those who underwent autologous SCT and 11 % for patients who did not.

COP-BLAM (cyclophosphamide, doxorubicin, vincristine, bleomycin, procarbazine, prednisone) and IMVP-16 (ifosfamide, methotrexate, etoposide)

A study evaluated patients with angioimmunoblastic lymphadenopathy-type lymphoma. Twenty-eight patients received only prednisone with 29 % CR (CI, 12–46 %), 18 received secondary prednisone with 56 % CR (CI, 33–79 %), and 11 received primary chemotherapy with COP-BLAM with 64 % CR (CI, 36–92 %) [90]. The median survival time was 15 months, with better response rates using chemotherapy than prednisone alone.

Histone deacetylase inhibitors (HDACI)

Vorinostat Vorinostat is a HDACI that was studied in AITL. Fourteen patients of mean age 55 years (range, 29–83 years) with 5 cases of AITL were treated with vorinostat along with CHOP. Two patients did not undergo response evaluation because of premature treatment termination. The remaining patients (93 %) achieved CR. The median response duration was 29 months, and mean follow-up time was 27 months. Four patients (3 AITL, 1 PTCL-NOS) experienced disease recurrence after having achieved CR. The 2-year PFS rate was 79 % and 70 % in all patients and in patients excluding ALCL, respectively. The median PFS duration was 31 months. The 2-year OS rate was 81 % and 75 % in all patients and in patients excluding ALCL, respectively. Adverse effects included hematological toxicity, diarrhea, and mucositis [91].

Romidepsin Romidepsin (depsipeptide or FK228), another HDACI, is one of the targeted therapies against T-cell lymphoma. Major and durable responses in CTCL supported the approval of romidepsin for CTCL. Romidepsin was administered as a weekly dose for 3 weeks on a 28-day cycle. Forty-seven patients, with median age of 59 years, with PTCL of various subtypes including angioimmunoblastic 6/47 (12.8 %), were enrolled. Exclusion criteria included CNS involvement, HIV infection, or prior therapy with a HDACI. There was one partial response (1/6, 16.7 %) for more than 23 months, making it a second-line treatment. Side effects included fatigue, nausea, vomiting, anorexia, and hematological suppression.

Belinostat Belinostat, one of the new HDACIs, has been studied in AITL and used as a single agent in refractory/relapsed lymphoma as daily infusions on days 1–5 every 21 days. The patient median age was 64 years (range, 29–81 years). AITL consisted of 10 of 22 (45.5 %) of patients with results notable for 25.8 % overall response (31/120), including 13 CR (10.8 %) and 18 PR (15 %), with an OS of 7.9 months [92]. Adverse effects were nausea, fatigue, and fever; severe reactions included acute kidney injury, thrombocytopenia, and toxic liver failure, with 7.8 % patients dying of drug reaction. Belinostat was determined to have a favorable hematological toxicity, although fatalities were seen because of drug-related tumor lysis syndrome, hepatic failure, and ventricular fibrillation from QTc prolongation [93].

DHAP/ESHAP combination regimens

DHAP (dexamethasone, cisplatin, cytarabine) was initially studied in a population with refractory lymphomas, with patients with median age of 55 years (range, 20–78 years) enrolled. Among the 54 patients enrolled with diffuse large-cell and immunoblastic lymphomas, 17 (31.5 %) achieved CR [94]. Adverse events included neutropenia, thrombocytopenia, sepsis associated with immunosuppression, and acute kidney injury. Another study evaluated 50 patients with 15 (30 %) determined to have diffuse immunoblastic lymphoma. Results with DHAP followed by high-dose carmustine, etoposide, cytarabine, and cyclophosphamide (BEAC) and autologous bone marrow transplant showed 40 % CR and 6.67 % PR in immunoblastic patients [95]. ESHAP (etoposide, methylprednsiolone, cytarabine, cisplatin) was also studied in refractory lymphoma with one study including 66 of the 122 patients (mean age, 53 years) enrolled to have intermediate-grade lymphomas including large-cell and immunoblastic lymphomas. In the intermediate grade, excluding large-cell lymphoma, 21 of 122 lymphomas were labeled as "Others," including immunoblastic, with 11 of 21 patients (51 %) attaining CR and 4 of 21 (18 %) achieving PR [96].

Gemcitabine

Gemcitabine had been studied in AITL as combination in GemOx (gemcitabine, oxaliplatin), GemOD (gemcitabine, oxaliplatin, dexamethasone) and GDP (gemcitabine, dexamethasone, cisplatin). GemOx was shown to produce an overall response of 45.8 % (11/24) in patients with refractory or recurrent lymphoma with 4 of 24 (16.7 %) CR and 7 of 24 (29.1 %) PR [97]. GemOD was studied in patients older than 60 years (median age, 65 years) with refractory T-cell lymphoma. Seven of 24 (29.2 %) were found to have AITL with 1 of 7 (14 %) with CR and 2 of 7 (28 %) with PR [98]. Toxicities included vomiting, paresthesias, and elevated creatinine and transaminases. GDP had been tested in treatment of refractory lymphoma, and one study consisted of 25 patients, of median age 54 years (range, 20–74 years), with 4 (16 %) AITL patients. There was no listed breakdown of cases, but the study found the overall maximal response rate after complete treatment to be 72 % with 48 % CR and 24 % PR [99]. Relapsed cases tended to be more responsive than primary refractory cases, although there was no statistical significance.

Bendamustine

Alternative single-agent regimens include bendamustine, a nitrogen mustard that works as an alkylating agent. One study analyzed patients with a median age of 66 years (range, 43–87 years) consisting of 32 of 60 (53 %) AITL patients. Results were notable for ORR of 28 % (95 % CI, 37–63 %) with 28 % CR and 22 % PR, without statistically significant difference in histology, age, gender, or the stage of disease [100].

Novel agents

Alemtuzumab (Campath-1H)

Alemtuzumab, an anti-CD52 monoclonal antibody, is a part of a new class of agents, humanized and chimerized monoclonal antibodies, and can be readily combined with full doses of cytotoxic chemotherapy. In one study, alemtuzumab was added to either CHOEP-14 or CHOP-14 depending on age, with AITL consistent of 26.8 % of the patients enrolled in the study. After pre-phase treatment (prednisolone/vincristine), patients <60 years of age received six cycles of CHOEP-14, and patients >60 years received six cycles of CHOP-14. Patients with CR or PR after chemotherapy received alemtuzumab consolidation starting 3–6 weeks after the end of chemotherapy. For patients who received alemtuzumab, the rate for EFS was 42.4 % (95 % CI, 23.8–61.0 %) and OS was 75.1 % (95 % CI, 59.0–91.2 %), which were clearly higher than in the whole cohort. After a median observation time of 46 months, 19 (46.3 %) patients have died, and death was mostly the result of lymphoma and/or salvage therapy complications [101].

Bortezomib

Bortezomib is a proteosome inhibitor, inhibiting the degradation of inhibitory kappa B and the activation of nuclear factor kappa B (NF-κB), which overcomes lymphoma resistance to apoptosis. Bortezomib in addition to CHOP was studied in 46 patients of median age 51 years (range, 21–66 years) with various types of T-cell lymphoma. Eight patients were diagnosed with AITL. Overall response was 87.5 %, with 6 (75 %) achieving CR and 1 (12.5 %) PR; 1 patient (12.5 %) had progression of disease. Five patients (62.5 %) were disease free at the end of the study. The median 3-year survival and progression-free survival of the whole group were 47 % and 35 %, respectively. Adverse events included neutropenia, infection, headache, fatigue, nausea, vomiting, diarrhea, liver dysfunction, and sensory neuropathy [102].

Brentuximab vedotin

Brentuximab vedotin is an antibody–drug conjugate (ADC) comprising an anti-CD30 antibody conjugated to

monomethyl auristatin E (MMAE) that binds to human CD30. After binding to the cell surface, the antibody induces cell death by induction of the apoptosis cascade [103]. Patients were treated with brentuximab vedotin with CHP (CHOP without vincristine to minimize neurotoxicity). Two of 39 (5.1 %) patients were diagnosed with AITL. Subset analysis revealed 54 % of AITL patients achieved an objective response, including 5 CRs and 2 PRs. At the time of analysis, median duration of response for all patients was 7.6 and 5.5 months for AITL patients, both with the same range of 1.3–14 months. Median duration of CR for all T-cell patients and for each subtype had not been reached at the time of this analysis. Those with AITL showed a median PFS of 6.7 months to date (range, 0.1–15.2 months) without apparent correlation between response and CD30 expression [104, 105].

Pralatrexate

Pralatrexate (10-propargyl-10-deazaaminopterin) is a novel antifolate and inhibits the recycling of 5,10-methylene tetrahydrofolate, which prevents the synthesis and precursors essential for DNA and RNA synthesis downstream [106]. One study that analyzed patients with refractory or recurrent lymphoma, which consisted of 13 of 111 (12 %) AITL patients, only 1 patient (8 %) had any response [107]. Another study comparing CHOP with cyclophosphamide, etoposide, vincristine, and prednisone (CEOP) with pralatrexate (CEOP-P) in peripheral T-cell lymphoma (PTCL) patients, which included 8 patients (24 %) with AITL, also found disappointing results [108]. Seventeen patients (52 %) achieved a CR with the 2-year progression-free survival of 39 % (95 % CI, 21–57) and overall survival of 60 % (95 % CI, 39–76), showing that CEOP-P did not improve outcomes compared to historical data using CHOP.

Anaplastic large-cell lymphoma (ALCL)

Incidence

Stein et al. first described anaplastic large-cell lymphoma (ALCL) after discovering that the Ki-1 monoclonal antibody can be used to identify neoplastic large lymphoid cells of T-cell lineage as well as Reed Sternberg cells of B-cell lineage [109]. There is a bimodal distribution with median age 24–27.5 years and again at 58–64 years [109, 110]. There is a predilection for men compared to women, 2:1, in ALCL with involvement of lymph node and skin in majority of patients, but also it arises in lung, gastrointestinal tract, or bone [110]. There is also primary cutaneous anaplastic large-cell lymphoma, first described in 1989 [111–113], which is associated with better prognosis [114,

115]. Other cutaneous forms of T-cell lymphoma are discussed later. ALCL is likely on the same spectrum of disease along with lymphomatoid papulosis and cutaneous Ki-1 lymphoma [116]. As with other T-cell lymphomas, anaplastic large-cell lymphoma can have CNS involvement [117, 118]. Of 1403 cases of NHL obtained worldwide in the International Non-Hodgkin's Lymphoma Classification Project, only 7 % represented a subtype of peripheral T-cell lymphoma (PTCL) and 2.4 % were anaplastic large T/null-cell lymphoma (ALCL). The ALK-positive subgroup consititutes 16 % of T-cell lymphoma in North America, 6.4 % in Europe, and 3.2 % in Asia, and an ALK-negative subgroup makes up 16 % in North America, 9.4 % in Europe, and 2.6 % in Asia [5]. Primary cutaneous ALCL makes up 5.4 % of T-cell lymphomas in North America, 0.8 % in Europe, and 0.7 % in Asia [5].

Breast implant-associated ALK-negative ALCL (BI-ALCL) was first described in 1997 in a woman with saline-filled breast implants [119]. Non-Hodgkin lymphomas of the breast are rare and comprise approximately 0.01–0.5 % of all malignant breast tumors; a recent study analyzing nonepithelial breast cancers found that of 106 patients only 1 was unspecified PTCL [120]. A recent review of BI-ALCL found that all patients were women, and the median age was 54 years (range, 28–87 years), with 58.6 % of those analyzed undergoing breast implants for cosmetic reasons and 41.4 % for breast cancer reconstruction. The median interval from implantation to diagnosis of BI-ALCL was 8 years (range, 2–25 years), with no difference between silicone and saline implant types [121].

Pathophysiology

The patterns of immunoreactivity of anaplastic large-cell lymphoma were found to be similar to Hodgkin's lymphoma, except that none were positive with B-cell antibodies but positive with T-cell antibodies, with all being positive for CD30$^+$ (BerH2$^+$) and TAL1B5 (anti-class II MHC), making them distinct [122, 123]. Anaplastic large-cell lymphoma is a subtype of nodal and extranodal lymphoproliferative disorder characterized by peculiar histopathological features and the positivity of lymphoid proliferating cells for Ki-1/Ber-H2 monoclonal antibody [111–113]. Biopsies of the lymph node usually show subtotal or sinusoidal involvement, and parenchymal fibrosis is common [114]. The large neoplastic cells are admixed with many reactive small lymphocytes, histiocytes, and/or neutrophils. Two cytological types of ALCL have been described: type I (pale cell) consisted of large polygonal cells with distinct pink-staining cell membrane and pale cytoplasm and pleomorphic nuclei showing marked chromatin clearing; and type II (basophilic cell) consisted of round or oval cells with basophilic cytoplasm and/or

paranuclear pale, pleomorphic nuclei often reniform or lobulated and with frequent multinucleated wreath-like and Reed–Sternberg-like cells [114]. Lymphocytes and granulocytes are significantly deficient in ALCL [124].

Expression of CD15 (more commonly in Hodgkins but can be seen in ALCL) [125], CD2, CD3, CD4, CD25, CD30 (Ki-1, BerH2), CD45, CD68, CD71, CD74, HLA-DR, EMA, vimentin, alpha-1-antichymotrypsin, BNH9, and restin are associated with ALCL [109, 126–135]. There are also associated beta- and gamma-TCR gene rearrangements in ALCL [136, 137]. Most of the patients will have stage III/IV disease at diagnosis with cytogenetic abnormalities in chromosome 2,5,7 [138]. Repeat case reports of t(2;5)(p23;q35) and t(3;5)(q12;q35) [139–141] lead to the isolation of fusion mRNA NPM-ALK (also known as p80$^{NPM-ALK}$), or other variant chimera X-ALK [142, 143]. Normal NPM protein is a non-ribosomal nucleolar phospho-protein involved with pre-ribosomal particles in both small and large ribosomal subunits. The NPM gene contributes an active promoter to drive expression of tyrosine kinase anaplastic lymphoma kinase (ALK) on 2p23, which is normally silent in lymphoid cells. The isolation of the chimeric protein led to the development of ALK1 or p80 antibody [144, 145] and fluorescent in situ hybridization (FISH) detection [146] with expression in 55–63 % of systemic ALCLs [145, 147–149]. ALK$^+$ ALCL is thought to derive from an activated mature cytotoxic T cell [150]. One recurrent translocation t(6;7)(p25.3;q32.3) is associated with the DUSP22 and IRF4 loci. The DUSP22 gene encodes a phosphatase, and its disruption is associated with upregulation of miR-29a and miR-29b on 7q32.3 [151]. ALK$^-$ ALCL has CD30 expression without ALK protein expression, likely a heterogeneous group of diseases classified by specific translocations [149, 151].

Cutaneous ALCL, histologically, have large and sometimes multinucleated cells with rounded or, more often, irregular nuclei containing nucleoli ranging from a large single nucleolus to small multiple nucleoli; the cytoplasm is usually abundant. Translocations involving the interferon regulatory factor 4 (IRF4) gene (also known as MUM1) have been described in a subset of cutaneous anaplastic large-cell lymphomas [152–154]. Because of their high growth fraction with lymph node extension, they are considered high grade and aggressive [155], and no precursor cell has been associated with the cutaneous subtype [143]. Breast implant-associated ALCL is defined as a T-cell lymphoma associated with a breast implant, with large, pleomorphic cells staining CD3$^-$, CD4$^+$, CD5$^-$, CD30$^+$, CD43$^+$, and ALK$^-$. The odds ratio is 18.2 (95 % CI, 2.1–156.8) for ALCL associated with breast implants [156]. In a study reviewing BI-ALCL, about 60 % of patients presented with an effusion around the implant, 20 % with a breast mass and effusion, 17 % with breast mass, and 3 % with neither [121]. Most had lymphoma confined to the capsule or just beyond the capsule but 15 % had lymph node spread [121, 157]. Pathogenesis is likely caused by inflammation, leading to polyclonal and eventually monoclonal lymphocytic activation against silicone, progressing to lymphoma [158]. Immune compromise may be a contributing factor to the development of ALCL, seen in cases after renal transplant, immunosuppressive therapy for Lambert–Eaton syndrome, and human immunodeficiency virus (HIV) [137, 159–161]. EBV is not a likely causal factor given studies have shown positive PCR but negative Southern blots [162, 163].

Types and classification

Results published from the International Peripheral T-Cell Lymphoma Project, a collaborative and international effort, helped us to better understand peripheral T-cell and natural killer (NK)/T-cell lymphomas (PTCLs). Of the 1314 eligible patients, 181 (13.8 %) had anaplastic large-cell lymphoma with characteristics listed in Table 2 [121, 149].

Table 2 Anaplastic large-cell lymphoma (ALCL): classifications and characteristics

Subtype	Systemic [149] ALK$^+$, (55 %)	Systemic [149] ALK$^-$, (45 %)	Primary cutaneous [149]	Breast implant associated [121]
Expression	CD30, TIA1, EMA, ALK$^+$	CD30, CD2, CD3, ALK-	CD30, CD2, CD3, ALK-	ALK$^-$
Patient	Male 1.7:1, median 34 years old	Male 1.5:1, median 58 years old	Male > female, median 55 years	Female, median 54 years, 8 years after implants
Labs	LDH elevated in 37 %, Hgb less than 110 g/l 27 %	LDH elevated in 46 %, Hgb less than 110 g/l 32 %	No data	No data
Disease	BM 12 %, bone 14 %, CNS 2 %, skin 8 %, lung 8 %, GI 18 %	BM 7 %, bone 7 %, CNS 0 %, skin 17 %, lung 13 %, GI 26 %	Skin, 5–10 % LN	As effusion or mass within capsule, invading outside, LN
FFS	60 %	36 %	55 %	NA
Five-year survival	70 %	49 %	90 %	89 %

Available treatments

Poor performance status, high stage, and elevated LDH were poor prognostic factors in both ALK$^+$ and ALK$^-$ ALCL. In contrast, increased age, multiple extra-nodal sites of involvement, and anemia (hemoglobin 110 g/l) were poor prognostic factors only in ALK$^-$ ALCL [149]. The isolation of the chimeric protein led to the development of an ALK-1 antibody [144] and the establishment of targeted therapy for ALCL [164]. Further clarification of NPM-ALK activity has elucidated that optimal levels are required in the cytoplasm and an excess of NPM-ALK signaling is detrimental to ALCL growth by triggering an oncogene-induced stress response and apoptosis. Nuclear sequestration of NPM-ALK is essential to maintain the optimal levels, and medication withdrawal leads to overproduction and subsequent apoptosis, suggesting a drug holiday may be warranted in the setting of drug resistance [165].

CHOP or CHOP-like therapies

In a retrospective Canadian study, of 33 of 199 cases of ALCL (17 %) identified with ALK protein status available for 30 patients (18 ALK$^-$, 12 ALK$^+$), cutaneous ALCL (CUT-ALCL) made up 8 % (n = 9). Patients mostly were treated with CHOP (91 % of the ALCL and 78 % of the CUT-ALCL). The CUT-ALCL had the best prognosis, with CR 89 % and 5-year OS 78 %. On CHOP, the ALK$^+$ group 5-year OS was 58 %, better than ALK$^-$ of which the OS was 34 %, although relapse was common for both groups. Three received autologous bone marrow transplant at relapse although only one remained in remission after 2 years [42]. CHOP and CHOEP were studied in patients with aggressive lymphomas; ALCL consisted of 3.5 % of the patients between 61 and 75 years old. Of all the patients, those with ALCL consititud 3.9 % of those who received CHOP-21, 3.4 % CHOP-14, 3.6 % CHOEP-21, and 3 % CHOEP-14. Complete remission rates for all patients were 60.1 % (CHOP-21), 70.0 % (CHOEP-21), 76.1 % (CHOP-14), and 71.6 % (CHOEP-14). Five-year event-free and overall survival rates were 32.5 % and 40.6 %, respectively, for CHOP-21 and 43.8 % and 53.3 %, respectively, for CHOP-14. In a multivariate analysis, the relative risk reduction was 0.66 (p = 0.003) for event-free survival and 0.58 (p < 0.001) for overall survival after CHOP-14 compared with CHOP-21. Because of its favorable efficacy and toxicity profile, CHOP-14 was recommended for patients ages 60 or older with aggressive lymphoma [81, 82]. A follow-up study comparing 18- to 60-year-old patients on CHOEP-14 of CHOEP-21, with 9.4 % ALCL of 139 patients (7.9 % of all patients on CHOP-21, 9.9 % CHOP-14, 10.8 % CHOEP-21, 9.1 % CHOEP-14), found that with high CHOEP-21, 63 of 78 (80.8 %) patients

achieved CR and 7.7 % PR while 9.0 % had progressive disease under treatment. After high-CHOEP-14, 27 of 41 (65.8 %) achieved CR and 12.2 % PR; 17.1 % had progression under therapy. Four-year EFS was 47.9 % after high-CHOEP-14 and 66.2 % after high-CHOEP-21, and 4-year OS was 62.1 % after high-CHOEP-14 and 73.4 % after high-CHOEP-21, respectively, suggesting a longer cycle may have better outcomes in patients younger than 60 years [82, 83].

In a study in which 90 ALCL patients were treated with F-MA-CHOP (vincristine, cyclophosphamide, fluorouracil, cytarabine, doxorubicin, methotrexate with leucovorin, prednisone) or MACOP-B (methotrexate with leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), the null phenotype was the most common with 39.8 % of the patients, while T cells accounted for 35.5 %. Complete remission (CR) was achieved in 66 of 90 (73.5 %) patients. The majority of the patients in CR (56.5 %) were alive and well at a median follow-up time of 38 months [166].

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)

Most patients with ALK$^+$ ALCL are potentially curable with doxorubicin-based chemotherapy, whereas patients with ALK$^-$ have a significantly lower survival. A study analyzed DA-EPOCH in 24 patients with untreated ALK$^+$ (15) and ALK$^-$ (9) ALCL who had similar characteristics. At follow-up after 14 years, the event-free survival in ALK$^+$ and ALK$^-$ was 72.0 % and 62.5 % (p = 0.54), respectively, and the OS was 78.0 % and 87.5 % (p = 0.83), respectively; the better OS in the ALK-group was surprising but the result may be inconsistent with known data due to small sample size. No treatment-related deaths were noted in the study, and only 10 % of patients had fever and neutropenia, suggesting tolerability with this regimen [167]. In another study where 21 patients were treated with DA-EPOCH, including 5 patients with anaplastic large-cell lymphoma (ALCL), the response rate of ALCL was 80.0 % (4/5); the CR rate was 40.0 % (2/5). The major toxicity was myelosuppression; the incidences of grade III–IV neutropenia, thrombocytopenia, and anemia were 34.3 %, 14.3 %, and 7.1 %. Other toxicities were mild; no treatment-related mortality occurred, and chemotherapy was well tolerated [168].

Stem cell transplant

A small study analyzed 16 patients (median age, 51.5 years) with recurrent ALK-negative who underwent high-dose chemotherapy and autologous stem cell transplant. Chemotherapy regimens include cyclophosphamide with total-body

irradiation, with thiotepa and etoposide, with carmustine and etoposide, with busulfan, or with etoposide and total-body irradiation. Of 15 patients, 13 relapsed after transplant; 1 patient was lost to follow-up. Median PFS for 15 patients was 12 weeks. Two-thirds of the patients died, with 9 of 10 of those patients dying of recurrent disease. Median survival was 72 weeks, and there was no transplant-related mortality [169]. In a retrospective analysis of 77 patients with T-cell lymphoma treated with myeloablative conditioning and allogeneic SCT after at least one previous treatment line (ALCL 27 of 77, 35 %), the 5-year OS and EFS rates were 57 % (95 % CI, 45–68 %) and 53 % (95 % CI, 41–64 %), respectively. According to the histopathological subtypes, the 5-year OS and EFS rates were 55 % (95 % CI, 35–72 %), and 48 % (95 % CI, 28–65 %) for ALCL patients with 5-year toxicity-related mortality (TRM) incidence of 33 % (95 % CI, 24–46 %) [170]. However, when adding brentuximab vedotin, allogeneic stem cell transplant survival seems to improve. In another small study, 8 of 15 (53 %) patients were studied using brentuximab vedotin. All 8 had a response, 7 of 8 with CR and 1 of 8 with PR. The 2-year PFS rate in this 15-patient case series (with ALCL and Hodgkin's lymphoma) was 66 %, and the median PFS has not yet been reached (range, 8.2–34.3+ months). The estimated 2-year OS rate was 80 % (95 % CI, 50–93 %), and adverse events included peripheral neuropathy [171].

Radiation and surgical resection for BI-ALCL

After 18 months of median follow-up, the 2-year overall survival rate for in situ and infiltrative BI-ALCL was 100 % and 52.5 %, respectively [157]. In a study analyzing therapy with and without surgery, 43 patients underwent limited surgery, 74 patients complete surgical excision, 51 patients systemic chemotherapy, and 39 patients radiation therapy. The most common chemotherapy regimen used was CHOP for six cycles. Other chemotherapy regimens include CHOEP, ABVD, and Hyper-CVAD. Of 43 patients who underwent limited surgery (not complete excision), the event rates were not different among the different pathological stages ($p = 0.44$). Among the 74 patients who had complete surgical excision, the rate of events was 14.3 % for patients with stage T4 and 0 % for patients with stages T1 and T2 ($p < 0.001$). Among the 51 patients who received systemic chemotherapy, the rate of events was 60 % for patients with T4 stage and was 13.3 % for patients with T1 stage ($p < 0.001$). Among the 39 patients who had radiation therapy, the rate of events was 56 % for patients with T4 stage and 0 % for patients with less involved stages ($p < 0.001$) [121]. Accordingly, this study showed a role for surgical resection or radiation in early-stage BI-ALCL compared to chemotherapy alone.

Future novel treatments

Crizotinib

Crizotinib is an ALK inhibitor against the common NPM/ALK fusion protein. For the first time, in 2011 two patients with chemotherapy-resistant ALK+ ALCL were treated with crizotinib. Both patients showed response, although the results were reported after only 6 months [172]. A follow-up study with 11 patients enrolled 7 men and 4 women (median age, 28 years; range, 19–55 years). Nine patients (82 %) had ALCL. In the ALCL group, 9 of 9 patients obtained CR (100 %; 95 % CI, 71.7–100 %), with 2-year PFS and OS rates of 63.7 % (95 % CI, 30.8–89.1 %) and 72.7 % (95 % CI 39.1–94.0 %), respectively. Adverse events included ocular flashes, peripheral edema, skin rash, erectile dysfunction, and hematological abnormalities [173]. However, ALK tyrosine kinase inhibition eventually leads to resistance, secondary to ALK gene mutation and amplification, bypassing downstream signaling via EGFR, KIT, SRC, or IGF-1R [174, 175]. In response, more drugs are being developed to overcome resistance [165, 176]. Second-generation ALK TKIs are in clinical trials, including certinib, alectinib, and brigatinib for ALK+ non-small cell lung cancer, but will likely be used for all ALK+ malignancies in the future [177].

Alisertib (SWOG 1108)

Aurora A kinase (AAK) is upregulated in highly proliferative lymphomas, suggesting its potential as a therapeutic target. Alisertib is a novel oral AAK inhibitor. Thirty-seven patients of median age 62 years (range, 21–86 years) with relapsed or refractory PTCL or transformed mycosis fungoides were treated with alisertib. Only 2 ALCL patients were enrolled in this study, with 1 patient achieving CR and the other showing stable disease. Adverse events included bone marrow suppression, mucositis, and rash. Vorinostat, the HDAC inhibitor for patients with PTCL, has been shown in cellular data to upregulate the expression of several pro-apoptotic genes, sensitizing cells to AAK inhibition [178], so current clinical trials are testing the efficacy of alisertib plus vorinostat or romidepsin (NCT01567709 and NCT01897012).

Bortezomib (Velcade)

Bortezomib in addition to CHOP was studied in 46 patients of median age 51 years (range, 21–66 years) with various types of T-cell lymphoma. Six patients

with ALK-negative ALCL were enrolled, and they all achieved a response with 4 (67 %) CR and 2 (33 %) PR. Four ALCL patients at the end of the study were without disease. The 3-year OS and PFS were 47 % and 35 %, respectively, for the whole group. Adverse events included neutropenia, infection, headache, fatigue, nausea, vomiting, diarrhea, liver dysfunction, and sensory neuropathy [102].

Brentuximab vedotin

In one study, patients were treated with brentuximab vedotin every 3 weeks, either sequentially followed by CHOP or in combination with CHP (without vincristine to minimize neurotoxicity). The study enrolled 32 of 39 (82 %) patients with systemic ALCL (6 ALK$^+$ and 26 ALK$^-$). Subset analysis revealed 13 of 32 received sequential treatment with 11 of 13 (85 %) achieving objective response, 8 of 13 (62 %) with CR and 3 of 13 (23 %) with PR. Nineteen patients received combination treatment with 19 of 19 (100 %) with objective response, 16 of 19 (84 %) achieving CR and 3 of 19 (16 %) PR. Six (46 %) patients with sequential treatment experienced progression of disease or death by 23.8 months with 1-year PFS of 77 % (95 % CI, 44–92 %) and 1-year OS of 85 % (95 % CI, 51–96 %). Nine of the 19 (47 %) ALCL patients with combination treatment experienced progression of disease or death. One-year PFS was 71 % (95 % CI, 49–85 %) and the 1-year OS rate was 88 % (95 % CI, 68–96 %) with CR patients maintaining their responses [104, 105]. Side effects included nausea, fatigue, diarrhea, alopecia, dyspnea, vomiting, and hematological suppression. Brentuximab resistance has been shown in lymphoma cells with downregulation of surface CD30 expression (although the effect is not permanent, and lymphoma cells have been noted to regain partial sensitivity after a drug holiday), and MMAE (the anti-microtubule agent that is the cytotoxic component of brentuximab vedotin) resistance had been noted through altered intracellular accumulation after internalization of the drug as well as increased MDR1 drug exporters [179].

Pralatrexate

One study that analyzed patients on pralatrexate with refractory or recurrent lymphoma consisted of 17 of 111 (16 %) ALCL patients revealed that 6 patients (35 %) achieved a response [107]. Another study comparing CHOP versus CEOP with pralatrexate (CEOP-P) in PTCL patients that included 4 of 28 (12 %) ALCL patients showed 50 % probability of 2-year PFS (95 % CI, 6–84 %) and 75 % probability of 2-year OS (95 % CI, 13–96 %) [108] in ALCL patients.

Vorinostat

Vorinostat was studied in ALCL, and in one study 14 patients (mean age, 55 years; range, 29–83 years), with 4 cases of ALCL, were treated with vorinostat along with CHOP. Two patients of the 14 did not undergo response evaluation because of premature treatment termination. The remaining patients (93 %) achieved CR. The median response duration was 29 months and mean follow-up time was 27 months. The 2-year PFS rate was 79 % and the 2-year OS rate was 81 % in all patients. Adverse effects included hematological toxicity, diarrhea, and mucositis [91].

NK/T-cell lymphoma

Incidence

NK cell lymphoma was first described in two patients with aggressive non-T and non-B lymphoma/leukemia in 1988, suggesting the existence of NK cell lymphoma. The leukemic cells possessed medium to large granules in the cytoplasm, antigens against CD2 and CD56 (NKH-1, N901) monoclonal antibodies on their cell surface, and also showed a high natural killer (NK) activity [180]. CD56 (NKH-1) expression is a rare phenomenon in malignant lymphomas, previously described as confined to the nasal or nasopharyngeal region, particularly in middle-aged men (mean age, 40 years), that were found to have a highly aggressive course [181]. NK lymphomas are now described as nodal or extranodal, including a nasal type, formerly called lethal midline granuloma [182]. In 1996 it was proposed that CD5$^-$ CD56$^+$ TCR silent PTCL should be categorized as a malignancy of NK cells [183]. Patients with nasopharyngeal lymphoma presented with skin, subcutis, GI tract, and testicular or non-nasal involvement [181, 183–186]. Extranodal NK, excluding the nasal type, is usually diagnosed at a later stage and seems to have a worse prognosis than the nasal type, which is more localized [184, 186]. NK/T-cell lymphoma constitutes 10.4–11.8 % of T-cell lymphomas, with 5.1 % in North America, 4.3 % in Europe, and 22.4 % in Asia, with male predominance 2:1 and median age of 49 years at diagnosis [5, 186]. Of NK/T lymphomas, 68 % are nasal, 26 % extra-nasal, and 6 % are unclassifiable [186].

Pathophysiology

NK cells are bone marrow-derived lymphocytes that mediate cytotoxicity without prior sensitization. There is no established causal etiology of all mature NK/T-cell

Table 3 Natural killer (NK) cell lymphomas: classifications and characteristics

Type	Nasal	Non-nasal	Lymphoma/leukemia
Sex	M > F	M > F	M > F
Median age	50–60 years	50–60 years	30–40 years
Site	Nasal, upper aerodigestive tract	Skin, GI, testis, soft tissue	Disseminated, liver, spleen, bone marrow, LN
Histology	Variable sized cells, nuclear folding, necrosis, angiocentricity	Variable sized cells, nuclear folding, necrosis, angiocentricity	Monotonous malignant cells, cytoplasm with azurophilic granules. Angiocentricity and necrosis in organs
Immunophenotype	$CD2^+$, $CD3^-$, cytoplasmic $CD3^+$, $CD16^-$, $CD56^+$	$CD2^+$, $CD3^-$, cytoplasmic $CD3^+$, $CD16^-$, $CD56^+$	$CD2^+$, $CD3^-$, cytoplasmic $CD3^+$, $CD16^{+/-}$, $CD56^+$
TCR	Germline	Germline	Germline
EBV	Most cases, clonal	Most cases, clonal	Most cases, clonal
Median survival	<12 months	<4 months	<2 months

malignancies transformed from NK cells. The Epstein–Barr virus (EBV) is associated with the nasal type, although usually infecting B cells, because EBV is present in patients with tumor cells containing clonal viral genomes in addition to detectable viral transcripts and protein. EBV DNA levels are elevated in most cases of extranodal nasal-type NK/T lymphoma, and the quantity at diagnosis and the pattern of detection during and after treatment have been shown to be predictive of outcome [187–191]. Localized nasal lymphoma have been shown to have diffuse infiltration by medium-sized to large abnormal lymphoid cells with irregular and pleomorphic nuclei in addition to angiocentricity and coagulative necrosis [184]. NK cells can be characterized by their immunophenotype. NK lymphoma cells express at least one of the T-cell antigens $CD2^+$, cytoplasmic $CD3^+$, $CD5^-$, and $CD56^+$, but are negative for TCR antibodies [183, 192]. TP-binding cassette subfamily C member 4 (ABCC4) levels have been found to be upregulated in human NK/T-cell lymphoma as compared with normal NK cells [193]. Molecular studies have shown deletion of 6q21, which contains tumor-suppressor genes such as FOXO3, PRDM1, and HACE1, causing dysregulation of NK cells and oncological pathway activation. JAK3 gene mutations seen in NK/T lymphoma also result in oncogenesis from JAK/STAT activation.

Types and classification

Kwong et al. categorized the NK cell lymphomas into three categories: nasal, non-nasal, and lymphoma/leukemia type (Table 3) [192].

Available treatments

A retrospective analysis of 172 patients with NK/T-cell lymphoma and aggressive NK-cell leukemia identified non-nasal disease, stage, performance status, and amount of extranodal involvement to be significant prognostic factors [194]. For nasal disease, significant predictors include stage, B symptoms, number of extranodal sites, and laboratory findings including LDH, hemoglobin, platelet count, and CRP in addition to high proliferation on histology [186]. Anthracycline-based chemotherapy alone is ineffective against NK lymphomas because of P-glycoprotein expression leading to multidrug resistance [195, 196].

Concurrent chemoradiotherapy (CCRT)

Concurrent chemoradiotherapy is the backbone for the treatment of early-stage NK/T-cell lymphoma [197]. One study enrolled 33 patients with a median age of 54 years (range, 20–69 years) with previously untreated extranodal NK/T-cell lymphoma, nasal type, who were treated with concurrent chemotherapy and radiotherapy. Of the 32 total assessable patients, 24 patients (75 %) achieved CR (95 % CI, 57–89 %): 1 with PR, 3 with SD, and 4 (12.5 %) with PD. The ORR was 78 % with local control achieved in 29 of 32 (91 %) of the patients. Treatments comprised concurrent radiotherapy (50 Gy) and three courses of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC). OS at 2 years was 78 % (95 % CI, 57–89 %). PFS at 2 years was achieved in 67 % (95 % CI, 46–81 %) of patients, with 10 of 27 (37 %) patients experiencing recurrence. Side effects included hematological suppression requiring blood transfusion and infection, weight loss, keratitis, and dermatitis [198]. Another study that enrolled 30 patients with median age of 48.5 years (range, 23–73 years), with nasal extranodal NK/T-cell lymphoma were treated with CCRT (radiation and cisplatin) followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD). After CCRT, 22 (73 %) achieved CR and 8 (27 %) PR. After VIPD chemotherapy, 19 patients retained CR, and 5 patients with PR to CCRT achieved CR. Twenty-four (80 %) patients achieved CR after the completion of VIPD

(95 % CI, 65.7–94.3), and 4 (13 %) of the 30 patients experienced disease progression. Three-year OS and PFS rates were 86.28 % and 85.19 %, respectively. Adverse events included hematological suppression, nausea, stomatitis, and neuropathy [199].

In a Chinese study, 38 eligible patients (median age, 40.5 years; range, 15–71 years), previously treated with CHOP or asparaginase/methotrexate/dexamethasone were enrolled for treatment with CHOP and L-asparaginase (CHOP-L) in addition to radiation. After treatment, 31/38 (81.6 %) of patients achieved CR, with 1 (2.6 %) PR, and 6 (15.8 %) PD after CHOP-L in combination with RT. The 2-year overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS) rates were 80.1 % (95 % CI, 73.3–86.9 %), 81 % (95 % CI, 74.5–87.5 %), and 93.6 % (95 % CI, 89.3–97.9 %), respectively [200]. Another study in which 13 patients of median age 62 years (range, 15–86 years) with nasal extranodal NK/T-cell lymphoma were treated with CCRT consisting of radiation and etoposide, steroid, high-dose cytarabine, and platinum (ESHAP), followed by monthly cycles of ESHAP alone, CR was achieved in 12 of 13 (92 %) patients, but 3 died secondary to relapse, sepsis, and pulmonary embolism. The remaining patient achieved a PR but developed progressive disease. Two-year OS was 72 % (95 % CI, 35–90 %) and FFP 90 % (95 % CI, 47–99 %). Adverse reactions were noted to be myelosuppression and mucositis [201].

To evaluate outcomes with less radiation, 40 Gy instead of 50 Gy, three prospective studies were evaluated with different consolidation chemotherapy regimens. Sixty-two patients (median age, 49 years; range, 26–79 years) were treated with VIPD, VIDL (etoposide, ifosfamide, and dexamethasone followed by intramuscular injection of L-asparaginase), and MIDLE (methotrexate, etoposide, ifosfamide, mesna, and L-asparaginase). Responses after completion of CCRT were CR in 56 patients (90.3 %), PR in 4 (6.4 %), stable disease in 1 (1.6 %), and progressive disease in 1 patient (1.6 %). The 5-year OS rate was 80.1 % (95 % CI, 66.2–88.7 %) and the 5-year PFS rate was 69.9 % (95 % CI, 53.7–86.1 %), with adverse events including GI complications such as nausea and mucositis [202]. Although overall response and overall survival were similar compared to the original study using 50 Gy, PFS with 40 Gy was found to be worse.

Sandwich chemoradiation

Another approach studied in the treatment of NK/T-cell lymphoma is undergoing radiation between chemotherapy treatments. In one study, 26 patients (median age, 43.5 years; range, 18–74 years) received L-asparaginase, vincristine, and prednisone (LVP) or CHOP, sandwiched with radiation therapy. After two cycles of chemotherapy,

radiation was started, and then chemotherapy was given for two to four cycles at 1 week after the completion of radiation. At the end of treatment, the ORR was 88.5 %, including 21 patients with CR (80.8 %; 95 % CI, 65.6–95.9 %), 2 with PR (7.7 %), and 3 with progression (11.5 %). Four patients followed the CHOP regimen instead of LVP because the L-asparaginase allergy skin test was positive. Adverse events included dermatitis, mucositis, nausea, vomiting, and abnormal liver function and blood counts [203]. Another study enrolled 35 patients with a mean age of 47 years (range, 21–74 years) with extranodal nasal-type NK/T-cell lymphoma to receive gemcitabine, L-asparaginase, and oxaliplatin (GELOX) induction chemotherapy for two cycles, followed by radiation therapy, and then chemotherapy for two to four additional cycles. At the end of treatment, the objective response rate was 96.3 %, which included 20 patients (74.1 %) who had CR and 6 patients who had PR (22.2 %). No disease progression during therapy was noted. Adverse events included myelosuppression, nausea, vomiting, liver dysfunction, mucositis, and dermatitis [204]. Finally, a study enrolled 63 patients with a median age of 65 years (range, 61–80 years) who received radiation sandwiched between chemotherapy, which included CHOP (18 cases, 30 %), pegaspargase plus gemcitabine and oxaliplatin (PGEMOX)/GELOX (16 cases, 26.7 %), and EPOCH (13 cases, 21.7 %) with a mean radiation dose of 54 Gy. The PGEMOX/GELOX regimen was associated with a significantly better treatment response than the other regimens in all patients (ORR, 87.5 % vs. 40.9 %, $p = 0.001$) and in stage I–II patients (ORR, 92.9 % vs. 51.6 %, $p = 0.008$). The PGEMOX/GELOX regimen improved the prognosis compared with other regimens in all patients, with 5-year OS of 75 % versus 16.7 % ($p = 0.002$) and 5-year PFS of 54 % versus 14.5 % ($p = 0.003$) [205].

Radiation

To determine the role of upfront radiotherapy, 82 patients (median age, 45 years) were treated with chemotherapy ($n = 8$, 9.8 %), radiation ($n = 9$, 11 %), or a combination ($n = 65$, 79.2 %). CR was achieved in 68 (82.9 %) of all patients, with 100 % of patients receiving only radiation achieving CR. The CR rates of the chemotherapy-alone group and the combination group were 25 % and 87.7 %, respectively. Initially, outcomes of patients receiving RT were better than those of other groups, but by 5 years, there was no difference with overall 5-year OS of 39.2 % [206]. In a Chinese study, 87 patients (median age, 43 years; range, 14–79 years) with stage I disease limited to the upper aerodigestive tract were enrolled to receive radiotherapy alone with a median dose of 50 Gy; 83 patients (95.4 %) achieved a CR and 2 (2.3 %) achieved a PR. The

5-year OS, PFS, and local control rates for all patients were 80 %, 69 %, and 93 %, respectively. Twenty (23 %) experienced disease progression or relapse [182]. Accordingly, it is established that radiation plays a crucial role in upfront treatment of NK/T-cell lymphoma patients.

SMILE (dexamethasone, methotrexate, ifosfamide, pegaspargase, and etoposide)

SMILE has been studied in the treatment of patients with NK/T-cell lymphoma. The first study to establish role of steroids with ifosfamide and asparaginase in treatment of NK/T-cell lymphoma enrolled 70 patients with a mean age of 48.5 years (range, 18–73 years) to be treated with ifosfamide, etoposide, methotrexate, and prednisolone (IMEP) plus L-asparaginase ($n = 22$) or combination chemotherapy without L-asparaginase ($n = 48$). Higher ORR and CR rates were observed in patients treated with IMEP plus L-asparaginase compared with those treated with chemotherapy without L-asparaginase (ORR, 90.0 % vs. 34.8 %, $p < 0.0001$; CR, 65.0 % vs. 21.7 %, $p = 0.001$) [207]. Subsequently, another study with 38 patients with a median age of 47 years (range, 16–67 years), with 20 patients having advanced disease, were treated with the SMILE regimen. Seventeen (45 %) patients had CR, 13 (34 %) had PR, 1 had no response, and 4 had progressive disease. Four (10.5 %) patients had early death. The OS rate at 1 year was 55 % (95 % CI, 38–69 %) and PFS at 1 year was 53 % (95 % CI 36–57 %). Adverse events included hematological suppression, infection, methotrexate-associated encephalopathy, and intestinal perforation caused by rapid tumor lysis as well as pancreatitis secondary to L-asparaginase [208].

AspaMetDex (L-asparaginase, methotrexate, and dexamethasone)

Another regimen that utilizes asparaginase in treatment of patients with NK/T-cell lymphoma is AspaMetDex. Along with methotrexate and dexamethasone, L-asparaginase was added because it is a drug with an antitumoral mechanism that is not affected by drug resistance. NK cells lack asparagine synthase activity, and asparaginase has been shown to induce apoptosis of tumoral NK cells in vitro. Of 19 patients (median age, 60 years; range, 45–77 years) included in the study, 11 (60 %) patients reached CR, 3 reached PR, and 6 patients relapsed. Both median survival time and median progression-free survival time were 12.2 months. Adverse events included hepatotoxicity, hematological suppression, infection, and renal failure [209]. A variation of this regimen uses high-dose methotrexate in combination with gemcitabine, pegaspargase, and dexamethasone (GAD-M) because pegaspargase and methotrexate are not affected by P-glycoprotein drug resistance [204].

Hematopoietic stem cell transplant (HSCT)

Stem cell transplant was studied in patients with refractory/relapsed NK/T-cell lymphoma. One study enrolled 40 patients with NK lymphoma who underwent hematological SCT with 25 patients receiving autologous and 15 receiving allogeneic stem cell transplant. Eleven patients had blastic NK-cell lymphoma and 22 had nasal-type extranodal NK-cell lymphoma. Before the transplant, 11 patients were refractory, 22 in complete remission, and 7 patients in relapse. Six patients died of transplant-related mortality, and patients who received HSCT when in CR had better prognosis than those who did not (58 % vs. 24 %, $p = 0.001$). The probability of relapse was lower for allo-grafted than auto-grafted patients (17 % vs. 29 %, respectively), but transplant-related mortality was higher for allo-grafted than auto-grafted patients (48 % vs. 4 %, respectively) [210]. Another study enrolled 28 patients with a mean age of 47 years (range, 19–68 years) who had failed prior chemotherapy (100 %) or radiation (32 %). Sixteen patients (57 %) underwent autologous stem cell transplant beyond complete remission. Most underwent BEAM or BEAM-like chemotherapy for conditioning before transplant. Response evaluation 100 days following transplant established that 24 patients (86 %) achieved CR, and 1 patient a PR (4 %); 2 patients never achieved CR, and 1 was non-evaluable. Fifteen patients (54 %) have died from relapse/progression of disease ($n = 7$), second malignancy ($n = 1$, cholangiocarcinoma), sepsis ($n = 1$), or unknown cause ($n = 2$); 4 deaths were attributed to complications of transplant. The 2-year PFS and OS estimates were 41 % (95 % CI, 26–64 %) and 52 % (95 % CI, 36–75 %) respectively. The 2-year PFS estimate for patients undergoing transplant in CR was 64 % (95 % CI, 41–100 %) compared to 25 % (95 % CI, 11–58 %) for patients not in CR ($p = 0.068$), suggesting transplant at CR yields better outcomes [211].

Future novel treatments

Alemtuzumab (Campath-1H)

Alemtuzumab-induced cytokine release appears to be a consequence of ligation of CD16 on NK cells. Previous studies have demonstrated that removal of CD56 NK cells, but not monocytes, abolishes the ability to mediate autologous antibody-dependent cell cytotoxicity; however, using alemtuzumab makes this reaction a potential therapy [212]. Alemtuzumab and EPOCH are being used to treat NK-cell lymphomas to see if there are improved outcomes (NCT00069238).

Bortezomib

Preclinical data of the combination of bortezomib and panobinostat (a HDACI) showed a potential therapeutic

approach in the treatment of NK/T-cell lymphoma. Bortezomib and HDACIs have also separately demonstrated activity in T- and NK/T-cell lymphomas in phase II studies, leading to their separate developments in phase III studies (NCT00901147). In peripheral T-cell lymphoma (PTCL), bortezomib inhibits cellular proliferation by downregulating microRNA 187, dephosphorylating ERK and Akt, and degrading MYC [213, 214]. However, when bortezomib was combined with CHOP in a phase II study in 46 patients with PTCLs of various histological subtypes, patients with NK/T-cell lymphoma, nasal type (10/46 patients, 21.7 %), responded poorly. The ORR was 40 % and the CR rate was 30 %, with 50 % of the patients experiencing progression of disease. Three-year OS and PFS were 47 % and 35 %, respectively, for the whole group. Peripheral neuropathy was the most important toxicity [102]. The combination of bortezomib and panobinostat was studied in 25 patients with PTCL in a clinical trial of which 23 patients were assessable for responses; 10 patients (43 %, 95 % CI, 23–63 %) had an objective response, of which 5 were CR. Adverse events included thrombocytopenia, neutropenia, diarrhea, fatigue, and peripheral neuropathy [215].

Bevacizumab (Avastin)

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) that is currently approved for the treatment of several solid tumors, including colon, lung, renal cell, and brain, with a recent study combined with CHOP to show effects on peripheral T-cell lymphoma. Of 39 patients (median age, 60 years; range, 21–81 years) who underwent treatment, the response rate was 90 % (CR 49 %), but the 3-year PFS and OS were disappointing with rates of 16 % and 37 %, respectively. Adverse effects include cardiac toxicity [216]. Currently, bevacizumab is being combined with GemOAD (gemcitabine, oxaliplatin, pegaspargase, dexamethasone) to be studied in patients with recurrent and refractory NK/T-cell lymphomas (clinical trial NCT01921790).

Siplizumab

Siplizumab is a humanized monoclonal antibody directed at CD2 with activity in the treatment of relapsed/refractory T-cell lymphoma, suggesting further development by combining it with cytotoxic chemotherapy. Siplizumab in combination with rituximab and EPOCH is being studied in clinical trials for relapsed/refractory lymphomas (NCT01445535). EBV lymphoproliferative disease was associated with the ability of siplizumab to deplete both T and NK cells in patients, so rituximab was added to prevent EBV reactivation in treating NK/T-cell lymphomas [217].

Cutaneous T-cell lymphoma

Incidence

Cutaneous T-cell lymphoma (CTCL) is a classification that encompass mycosis fungoides, Sezary syndrome, and related lymphoproliferative disorders that originate in the skin with systemic involvement [218]. Mycosis fungoides and Sezary are both T-cell malignancies with similar cytological and histological features; progression from small plaques to cutaneous tumors may lead to eventually involvement of lymph nodes and viscera. Based on SEER date, incidence of CTCL is 7.7/1,000,000 person-years [219]. CTCL is associated with a median age at diagnosis in the mid-fifties, male predominance (male-to-female ratio, 1.7:1), and a higher incidence in African Americans [220, 221]. Overall survival of CTCL was 63 months, with 1-, 2-, and 5-year survival rates of 88 %, 77 %, and 52 %, respectively [220]. CTLC consists of a diverse group of diseases. Mycosis fungoides, first described by Jean Louis Alibert in 1806, named because of the cutaneous mushroom-like appearance, was found to have involvement of lymph nodes, blood, and viscera [222]. Patients with mycosis fungoides (MF), the most common CTCL, classically present with patches, plaques, tumors, and ulcers [218]. Pagetoid reticulosis, first described in 1939 by Woringer and Kolopp, is a variant of MF and presents as localized, hypertrophic, or verrucous lesions on extremities [223]. Folliculotrophic MF is another type that presents with hair loss, known as alopecia mucinosa [223]. Sezary syndrome, first described in 1938, is characterized by exfoliative erythroderma, lymphadenopathy, and circulating diagnostic cerebriform cells, known as Sezary cells [222]. It is a rare leukemic variant with high mortality and median overall survival of 5.1 years [224]. Patients may present with pruritis as well as skin lesions on the face that can be hyperpigmented, producing lion-like faces with ectropion formation leading to ocular inflammation [218, 225]. Lymphomatoid papulosis is a CD30^{+} lymphoproliferative disorder with a self-regressing clinical course that is associated with increased risk of lymphoma [226].

Pathophysiology

CTCL is an indolent, epidermotrophic CD2^{−} CD3^{+} CD4^{+} CD5^{−} CD7^{−} CD8^{−} CD45 Ro^{+}, CCR4^{+} T-cell lymphoma characterized by eczematous or psoriasiform skin lesions as seen in mycosis fungoides (MF) or by diffuse erythroderma and circulating atypical lymphocytes as seen in Sezary syndrome (SS) [221, 223]. MF and SS were both determined to be derived from T-cells; more specifically, MF from the tissue-resident memory cells localized

in the skin compared to SS from the central memory cells or regulatory T-cells, which can access peripheral blood and explains the leukemic nature of SS [225, 227–231]. MF histologically presents with a dense infiltrate of atypical lymphoid cells with hyperchromatic convoluted nuclei and scant cytoplasm within the upper dermis, with the epidermis containing similar cells in aggregates known as Pautrier microabscesses [223]. Pagetoid reticulosis histologically shows cytologically atypical mononuclear cells that exhibit epidermotropism with a clonal rearrangement of the beta T-cell receptor gene compared to folliculotrophic MF, which presents with alopecia because of the tumor infiltration of hair follicles with deposition of mucin [223]. Sezary described the pathognomonic feature of SS as "cellules monstrueues," monstrous cells greater in size than a polymorphonuclear leukocyte, with a voluminous, irregularly shaped nucleus occupying 80 % of the cell and around which the cytoplasm forms a thin crown. There is evidence that CTCL is caused by chronic antigen stimulation with the protumorgenic role of mast cells and macrophages in CTCL from an infectious etiology or medication [221, 224, 225, 229, 231, 232]. Tumor-associated macrophages (TAMs), the most frequently found leukocyte population within the tumor microenvironment, produce distinct biochemical and cytokine profiles in many types of tumors, with low IL12, high IL10, and VEGF driving angiogenesis [233]. *Staphylococcus aureus* has been hypothesized to be related to CTCL pathogenesis, with an association between it and CTCL, as disease improvement is noted with bacterial eradication and changes in T-cell receptor Vb consistent with superantigen stimulation [234, 235]. Although Merkel cell polyomavirus and HTLV-1 have been found not to be the causal oncogenic virus in CTCL, there is evidence for oncogenic infectious agents because infectious disease pathways are upregulated [236–238]. Hydrochlorothiazide is associated with MF, supported by recession of disease with discontinuation of the drug and recurrence with re-initiation; the mechanism is possibly from the chlorine atom dissociated by UVB to create free radicals [239]. STAT3 was found to be activated, leading to abnormal growth regulation in tumor cells and resistance against apoptosis [240, 241]. FAS deficiency as well as overexpression of TOX, PLS3, KIR3DL2, ITGB1, PDCD6, TP53, RB1, PTEN, DNMT3A, CDKN1B, MAPK1, BRAF, CARD11, and PRKG1 are also found to be molecular mechanisms responsible for acquired resistance to apoptosis and oncogenesis in CTCL [224, 242–246].

The miRNAs are a class of small noncoding regulatory RNA molecules that repress translation [247]. miR-150 inhibits metastasis and invasion; miR-16 induces senescence in cancer cells. Tumor suppressive miRNAs, including miR-16, miR-29a, and miR-150, were found to be suppressed in advanced CTCL and various NK/T-cell lymphomas [248]. Abnormalities associated between 1p22 and 1p36 is a region that may be involved in malignant progression [249]. Additional cytogenetic abnormalities, involving gains of chromosomes 1q and 8q and losses of chromosome 10q, have been associated with inferior survival [221]. Of note, higher proportions of dermal CD30- and dermal Ki-67-positive lymphoid cells were significantly associated with large-cell transformation and a higher stage at diagnosis [250].

Types and classification

The WHO-EORTC classification for cutaneous lymphomas includes mycosis fungoides, Sezary syndrome, and others including primary cutaneous peripheral T-cell lymphoma, not otherwise specified (NOS) as listed in Table 4 [251].

Available treatments

Primary cutaneous CD30-positive lymphoproliferative disorders are the second most common form of cutaneous T-cell lymphomas and include lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Consensus recommendations from the European Organization for Research and Treatment of Cancer, International Society of Cutaneous Lymphoma, and United States Cutaneous Lymphoma Consortium for the treatment of primary cutaneous CD30^{+} lymphoproliferative disorders are summarized as follows: for lymphomatoid papulosis, therapies include observation, PUVA, systemic methotrexate, and topical steroids.

The focus of this review is to discuss the available and novel treatments of patients with MF, SS, and CTCL, keeping in mind that a more advanced disease stage, older age (more than 60 years), absent folliculotropism, large-cell transformation in skin, elevated WBC, and elevated LDH are worse adverse prognostic factors in MF and SS, and that these patients require more aggressive treatment [220].

Topical treatments

Topical steroids   Topical steroids have been used for the treatment of patients with MF. In one study, 79 patients with a median age of 60 years (range, 14–84 years) with stage T1–T2 MF were treated with topical steroids twice daily for at least 3 months. More stage T1 patients (63 %) than T2 patients (25 %) achieved CR, but overall response was not significantly different with stage T1 (94 %) compared to stage T2 (82 %). Relapse was common; CR in T1 went from 63 % at maximum response to 37 % at time of last follow-up and T2 from 25 % to 18 %. Adverse events included depressed serum cortisol as well as cutaneous atrophy and

Table 4 Cutaneous T-cell lymphoma (CTCL) classifications

Types	Behavior	Frequency (%)	Percent (%) 5-year survival
Mycosis fungoides (MF)	Indolent	44	88
Folliculotropic MF	Indolent	4	80
Pagetoid reticulosis	Indolent	<1	100
Granulomatous slack skin	Indolent	<1	100
Sezary syndrome	Aggressive	3	24
Adult T-cell leukemia and lymphoma	NA	NA	NA
Primary cutaneous CD30$^+$ lymphoproliferative disorders			
Primary cutaneous ALCL	Indolent	8	95
Lymphomatoid papulosis	Indolent	12	100
Subcutaneous panniculitis-like T-cell lymphoma	Indolent	1	75
Extranodal NK/T-cell lymphoma, nasal type	Aggressive	<1	NR
Primary cutaneous peripheral T-cell lymphoma, nos	Aggressive	2	16
Primary cutaneous aggressive epidermotropic CD8$^+$ T-cell lymphoma	Aggressive	<1	18
Primary cutaneous CD4$^+$ small/medium pleomorphic T-cell lymphoma	Indolent	2	75

irritation [252]. A follow-up study with the usage of clobetasol found that in more than 200 patients, overall response rate continues to be greater than 90 % in stage T1 and above 80 % in stage T2 MF patients [253].

Nitrogen mustard Nitrogen mustard was used in the past for the treatment of MF. In one study in which 203 patients (median age, 56 years; range, 12–87 years) received topical nitrogen mustard, 83 % responded, with 102 patients (50 %) achieving CR. Of patients with CR, 43 (41.7 %) experienced relapse, 70 % within 2 years. Patients with T1 were more likely to achieve CR, as seen in 70 patients (65 %) compared to 30 patients with T2 (34 %). The 5-year survival rate was 85 % with a median survival of 16.3 years. Patients with T1 had a 5-year overall survival of 97 % compared to T2 with 72 %. PFS rates were 91 % for T1 and 93 % for T2 at 20 years. Adverse effects included irritant or allergic contact dermatitis and, rarely, skin cancer [254]. Mechlorethamine (methyl-bis[2-chloroethyl]amine) hydrochloride, commonly known as nitrogen mustard, is an alkylating agent that was used in 260 patients with a median age of 58 years (range, 11–88 years) with MF up to stage IIA. The overall response rate was higher for the gel treatment arm (58.5 %) than for the ointment treatment arm (47.7 %). Adverse effects included local skin irritation, which was noted to be worse in the gel form [255].

Local radiation Radiation is rarely used anymore, but it was tried in a few studies. In one study, 21 patients (median age, 55 years; range, 27–73 years) with untreated or recurrent stage IA MF were enrolled for local superficial radiation (LSR). Median surface dose was 20 Gy (range, 6–40 Gy) with a CR rate of 97 %, and all patients were alive at the last evaluation. Disease-free survival (DFS) was 75 % at

5 years and 64 % at 10 years, with DFS of 91 % at 10 years when treated with radiation greater than 20 Gy. Adverse effects included mild erythema, dermatitis, telangiectasias, and dry desquamation without reports of secondary malignancy [256]. In a larger study, 270 lesions were treated with radiation in 58 patients (median age, 62 years) with various stage I–IV CTCL, including 47 MF, cutaneous gamma-delta T-cell lymphoma, SS, and small/medium-sized pleomorphic T-cell lymphoma. The majority (97 %) were treated with ≥700 cGy, with the best response in lower-extremity lesions. CR was found in 255 (94.4 %) lesions, PR in 10 (3.7 %) lesions, a PR converted to a CR after a second treatment in 4 (1.5 %) lesions, and no response in 1 (0.4 %) lesion with a mean follow-up of 41.3 months (range, 3–180 months). Adverse effects were mild skin reactions [257].

Topical bexarotene Bexarotene gel, which binds retinoid X receptors for antineoplastic properties, is used for treating early CTCL. In one study 67 patients (median age, 61 years; range, 30–87 years) with stage IA–IIA CTLC were enrolled; and of note, 55 of the patients enrolled had failed previous therapy. Patients with SS, visceral involvement, lymphadenopathy, or tumors were excluded. Overall response to bexarotene gel was 63 % with CR in 21 % of the patients (95 % CI, 50–74 %). Of 42 responding patients, 17 (40 %) relapsed, but 13 (31 %) responded again with maintenance therapy. Adverse effects included dermal pain, edema, and rash with one incidence of trigeminal neuralgia of undetermined origin [258]. In another study, 55 patients were enrolled (median age, 64 years; range, 13–85 years, and stage IA–IIA CTCL) to be treated with bexarotene. Overall response was seen in 27 of 50 (54 %) patients (95 % CI, 39–68 %) with CR in 5 of 50 (10 %). Seven of the 27 (26 %) responders, however, relapsed.

Adverse effects included local dermatitis, pruritus, pain, and inflammation.

### Phototherapy (UVB and PUVA)	Ultraviolet-B phototherapy (UVB)

Disease confined to the skin can be treated with phototherapy, such as using ultraviolet B. In one study, 24 patients with patch-stage MF were treated, with 13 (54.2 %) patients achieving CR, 7 (29.2 %) PR, and 4 (16.7 %) no response. Four patients with CR relapsed with mean time to relapse of 12.5 weeks [259]. In another study with 58 patients who received UVB (emitted UVB of 280–350 nm) either with home UVB or home and office UVB, 31 patients of 58 (53.4 %) who underwent home UVB achieved a response compared to 10 of 10 (100 %) that received home and office therapy. Maintenance therapy was continued if using home UVB with relapse was common when discontinued. Minimal data report improvement in outcome when UVB is combined with bexarotene. Adverse events include ocular effects [260].

PUVA: oral psoralen and UVA

8-Methoxypsoralen (MOP) was first used in 1976 for MF, thought to work by inhibiting DNA synthesis causing direct cytotoxicity and immunological alterations in skin lesions. One study that enrolled 104 patients with stage IA–IIA MF showed 66 (63.4 %) patients achieved CR. Relapse was seen in 33 patients with a median disease-free interval of 39 months (range, 5–238 months). Disease-free survival rates at 5 and 10 years were 56 % and 30 % for stage IA and 74 % and 50 % for stage IB/IIA, respectively. Adverse effects included photo damage and secondary skin cancers [261]. A review found that 58–100 % of MF patients treated with PUVA achieved CR with varying degrees of relapse. In some patients with early MF, a CR of up to 6 years may be sustained without maintenance therapy. During the follow-up period in one study, 50 % maintained a CR and 50 % experienced relapse. Adverse effects include erythema, fatigue, headache, photosensitivity, nail changes, photoaging, and skin cancer [260]. In a retrospective comparison study of 114 patients with early-stage (IA–IIA) MF, 95 patients (mean age, 59 years; range, 30–80 years), were treated with PUVA and 19 patients of mean age 68 years (range, 31–87 years) were treated with UVB. PUVA led to CR in 59 of 95 (62.1 %) and PR in 24 of 95 (25.3 %) patients compared to the UVB CR of 13 of 19 (68.4 %) and PR of 5 of 19 (26.3 %) patients. Adverse events included skin burning, erythema, blisters, and GI complaints in the PUVA group compared to skin burning in the UVB group [262]. However, another study suggests that thick plaques or folliculotropic involvement may be better served by PUVA than UVB because of superior penetration [260].

Total skin electron beam therapy (TSEBT)   Treatment with TSEBT (mostly 36 Gy) with topical nitrogen mustard compared to topical mustard alone was studied in 148 patients of median age 58 years (range, 19–87 years), with T2 or T3 MF without lymphatic, hematological, or visceral involvement. Overall CR was found in 57 % of the T2 cohort (76 % TSEBT with nitrogen mustard, 39 % mustard alone) and in 33 % of the T3 cohort (44 % with both, 8 % with mustard alone). Freedom from progression rate for TSEBT and topical mustard was 41 % compared to 39 % for topical mustard alone. Overall median survival was 11.7 years for T2 compared to 5.1 years in T3. Adverse events included skin cancer and cardiopulmonary disease [263]. In another study, TSEBT (24–34 Gy) was studied in 57 patients (median age, 61 years; range, 18–82 years) with T1 or T2 MFwas studied. At 3 months, overall response was seen in 54 patients (94.7 %), with 50 patients (87.5 %) of the T1 group and 48 patients (84.8 %) of T2 achieving CR and 4 (8.77 %) achieving PR. All patients had relief of their pruritus. Relapse occurred in 31 patients (54 %). Overall survival was 90 % at 5 years, 65 % at 10 years, and 42 % at 15 years. Adverse effects included skin toxicities, edema, reversible alopecia, xerosis, telangiectasies, nail changes, as well as second malignancies of unknown origin [264]. Comparison studies for conventional dose (36 Gy) and lower dose therapies (<30 Gy) have been done with worse response but better side effect profiles. In one composite study, 33 patients of median age 63 years (range, 19–83 years) were studied using low-dose TSEBT (12 Gy). The ORR was 88 % with 9 (33 %) patients achieving CR and 4 (12 %) achieving PR [265]. This comparison was also studied in 45 patients with MF, SS, and other CTCL using a conventional dose (30–36 Gy) and a low dose (<30 Gy). ORR of 92 % with 50 % CR was seen in MF patients, ORR 70 % with 50 % CR in SS patients, and ORR 89 % with 78 % CR in non-MF/SS CTCL patients. OS was 77 months in MF and 48 months in SS with conventional dose regimens, compared to 14 months in MF and 16 months in SS with lower dose, demonstrating dose response. Median PFS for a conventional dose was 15 months in MF and 19 months in SS, compared to low dose, which was 8 months in MF and 3 months in SS [266]. Also confirming that a conventional dose >30 Gy is more efficacious, 102 patients of median age 59 years (range, 21–90 years) with MF were treated with radiation doses of 5 to <10 Gy (very low), 10 to <20 Gy (low), and 20 to <30 Gy (medium). With T2–T4 disease, CR were 16 % in the very low dose, 35 % in the low dose, and 34 % in the medium dose, compared to 62 % at the conventional >30 Gy dose. Clinical response was seen in 96 % of patients, and response rates were higher among those with earlier-stage disease or those receiving higher doses of radiation [267]. These studies reported adverse effects as temporary alopecia, dermatitis, edema, pain, nail changes, and fatigue.

Systemic treatment (more advanced stages)

Oral bexarotene (Targretin)   Retinoids belong to the steroid hormone family of molecules and are physiological regulators of a large number of essential biological processes including embryonic development, vision, reproduction, bone formation, metabolism, hematopoiesis, differentiation, proliferation, and apoptosis. Bexarotene, the oral or topical RXR-selective rexinoid, promotes cell-cycle arrest and apoptosis. In one study, 58 patients of median age 64 years (range, 24–86 years) with stage IA–IIA refractory CTCL were treated with oral bexarotene. The overall response was 48.2 %, although this improved to 58 % with doses greater than 300 mg/m^2. Clinical complete responses occurred in 2 (7 %) of the 28 patients with 300 mg/m^2 and in 4 (27 %) of the 15 patients with >300 mg/m^2. Adverse events included headache, hypothyroidism, hematological suppression, infection, and hypertriglyceridemia [268]. In another study, 94 patients of median age 64 years (range, 27–89 years) with IIB–IV CTLC were treated with bexarotene at 300 mg/m^2/day. The overall response rate was 45 % (25 of 56) of patients starting at 300 mg/m^2/day and in 55 % (21 of 38) of patients at higher doses. CR occurred in 2 % (1/56) of the patients at 300 mg/m^2/day and in 13 % (5/38 patients) at the higher doses. Adverse events were similar to the previous [269]. It was noted that patients taking two lipid-lowering medications had a higher response rate of 90 % during monotherapy, suggesting that the treatment of adverse effects of bexarotene can prolong response [270]. In a combination trial with interferon, 22 patients with median age 57 years (range, 22–79 years) with stage refractory IB–IV CTCL were treated with oral bexarotene and subcutaneous interferon-alpha. The overall response rate was 39 % (95 % CI, 17–64 %), including 1 patient with a CR, 6 patients with PR, 3 patients with stable disease, and 8 patients with progressive disease. The addition of interferon-alpha did not increase the response rate that would have been expected with bexarotene alone, and accordingly such combination is not recommended [271].

Interferon   Interferons were named by Isaacs and Lindemann in 1957 based on their ability to "interfere" with viral replication in infected cells. Interferon-alpha inhibits IL-4 production in both normal T cells and Sezary cells. In one study, 22 patients with stage I–IV CTCL who were treated with interferon-alpha (IFNα) showed an ORR of 64 % with 3 CR, 10 PR, and 1 minor response. An objective response was seen in 73 % of the patients with stage IA–IIA CTCL compared to 60 % of those with stage IIB–IVA disease. Adverse events included malaise, fatigue, depression, anorexia, and weight loss [272]. Interferon-alpha was also evaluated in another study with 51 patients enrolled (median age, 56.8 years; range, 15–74 years), and results showed

CR in 21 (41 %) patients and PR in 13 (25 %). The study also showed that 17 patients had stable or progressive disease (34 %); 12 (57 %) of the 21 patients in CR had relapse within a mean period of 7.5 months. Adverse effects were similar as noted previously [273]. IFNα is also used in combination with other external, cytotoxic, or immunomodulating agents with overall response rates of 42–86 % [274]. Given Fas deficiency in CTCL, interferon-alpha and methotrexate upregulate Fas via different mechanisms. Interferon-alpha acts through the JAK-STAT signal transduction pathway, enhancing Fas protein expression and sensitivity to Fas pathway apoptosis [275]. A study of refractory MF and SS treated with a combination of INFα and methotrexate enrolled 158 patients with a median age of 63.4 years (range, 18–83 years) found that by 12 months, 112 (74 %) achieved CR but 52 (47 %) of those cases relapsed. Forty patients died of tumor progression and 8 of treatment toxicity; 10-year overall survival was 69 %. Adverse events included flu-like syndrome, granulocytopenia, and transaminitis [276].

Interferon was also combined with PUVA in one study of 89 patients with median age 60 years (range, 17–80 years) with stage I–IIA MF; 75 (84.2 %) patients achieved CR but 28 (37 %) patients of 75 experienced a relapse with median time to relapse of 46 months. At the last follow-up, 87 patients were alive; 64 (72 %) had CR, 20 (22.4 %) PR, 2 (2.2 %) no response, and 1 (1.2 %) progression of disease. The OS rate was 90 %, and disease-specific survival was 100 % at 9 years. At 12 months, 85 % of patients were still event free, decreasing to 54 % at 36 months and to 23 % at 72 months. Relapse and treatment intolerance were the principal factors. Adverse events included GI toxicity, secondary malignancy, fatigue, and flu-like syndrome as well as hematological toxicity, thyroid dysfunction, and depression [277]. In another study, 96 patients with stage I–II pleomorphic T-cell lymphoma or MF received IFN with PUVA or acitretin. Forty patients with median age 58.8 years (range, 30–81 years) were treated with IFN and PUVA compared to 42 patients of median age 58.4 years (range, 26–82 years) who were treated with IFN and acitretin. Overall response was 80.0 % in the IFN + PUVA group, with 28 of the 40 (70.0 %) patients achieving a CR and 4 patients achieving PR, which was better than the acitretin group. Overall response in the IFN + acitretin group was 59.5 %, with 16 of the 42 (38.1 %) patients with CR and 9 with PR. Side effects included flu-like symptoms, bone marrow suppression, gastrointestinal disorders, and elevation of triglycerides (retinoid group) and liver enzymes [278]. Interferon was studied in combination with phototherapy, and in one study 15 patients with MF/SS were enrolled to undergo treatment with phototherapy and systemic IFNα. The overall response rate was 90 % with 24 (62 %) CR and 11 (28 %) PR. The median duration

of remission for patients who achieved CR was 60 months compared to 13 months in patients who achieved PR. The median survival duration for the entire cohort was 62 months. The mean survival time for stage I–II patients was 55 months compared to 35 months in stage III–IV. Adverse effects included impotence, anorexia, weight loss, renal failure, and dyspnea [279].

Histone deacetylases inhibitors (HDACIs) The histone deacetylase (HDAC) inhibitors target not only the epigenome via histone modification, but also numerous nucleic and cytoplasmic nonhistone proteins, to induce cancer cell apoptosis and to modify the tumor microenvironment. Romidepsin (depsipeptide, FK228) is an HDACI isolated from *Chromobacterium violaceum* and found to have antitumor effects through gene modulation. In one study 71 patients of median age 57 years (range, 31–77 years), with mostly refractory/relapsed stage I–IV CTCL were treated with intravenous romidepsin. The overall response was 34 %, with 4 (7 %) achieving CR and 20 (26 %) with PR. Twenty-six (38 %) had stable disease and 15 (17 %) experienced progression. Adverse events included hematological suppression, nausea, fatigue, vomiting, anorexia, and EKG changes (T-wave flattening, ST depression) [280]. Another study enrolled 96 patients with a mean age of 57 years with stage IB–IV CTCL to be treated with romidepsin. Similarly, the overall response rate was 34 % with 6 (6.3 %) CRs [281].

Another HDACI, Vorinostat (suberoylanilide hydroxamic acid, SAHA, Zolinza), was tried in the treatment of CTCL. Vorinostat is an oral HDACI that was shown to induce cell-cycle arrest and apoptosis. Thus, 33 patients (median age 67 years; range, 26–82 years) with stage IA–IV CTCL were enrolled in one study to be treated with Vorinostat. No patients achieved CR, but 8 (24.2 %) achieved PR. Six of the responders developed progression of disease. Adverse effects included fatigue, diarrhea, nausea, thrombocytopenia, dysgeusia, and dry mouth [282]. Another study enrolled 74 patients of median age 60 years (range, 39–83 years) with IB–IV stage CTCL to be treated with vorinostat. The overall response was 29.7 %, with 1 patient achieving CR after 9 months. The median time to response was less than 2 months, and the median time to progression was less than 5 months. Adverse events were similar as previously noted, with follow-up study reporting safety and tolerability of long-term therapy greater than 2 years [283, 284].

Extracorporeal photopheresis (ECP, UVAR) First done in 1987, extracorporeal photochemotherapy involves patients taking oral methoxsalen and then undergoing leukopheresis/plasmapheresis so their pre-medicated blood is exposed to UVA to form cross-linked DNA before returning to the body for induction of apoptosis [285]. ECP leads to mono-

cyte activation, dendritic cell differentiation, and initiation of host immune response [260]. In the initial study, 27 of 37 patients responded to treatment without bone marrow suppression, GI complaints, or alopecia [285]. Twenty patients with a mean age of 61.2 years (range, 29–85 years) at diagnosis of CTCL were studied with an overall response of 55 %, with 7 (35 %) CR, 4 (20 %) PR, and 8 (40 %) with progression of disease and 1 (5 %) with stabilization of disease. Adverse events included nausea, hypotension, hypoglycemia, and hematomas without any incidence of infection [286]. A review of 438 patients with MF/SS who underwent ECP found that 244 of 438 (55.7 %) had a significant response. Adverse reactions are rare and are most likely related to discomfort or hematomas at the venipuncture site, but sepsis, disseminated fungal infections, herpes infection, thrombophlebitis, secondary skin cancer, and machine-induced sepsis have been noted [287]. ECP had been studied also in combination with TSEBT in a study that enrolled 44 patients of median age 68 years (range, 29–82 years) with erythrodermic MF to be treated with TSEBT (32–40 Gy) and ECP. Thirty-two (73 %) patients achieved CR with a 3-year DFS of 63 %. The 2-year PFS, cause-specific survival, and OS for the TSEBT group were 36 %, 69 %, and 63 %, respectively, compared with 66 %, 100 %, and 88 %, respectively, for the TSEBT in combination with ECP group. Thirteen patients were noted to die of MF-related causes and 8 to die of other causes [288]. ECP was also studied with systemic treatment combinations, and in one study 73 patients with SS underwent treatment with extracorporeal photopheresis and systemic immunostimulatory agents, including IFNα, IFNγ, TSEBT, PUVA, UVB, chemotherapy, prednisone, GM-CSF, and retinoids. The overall response was 75 %, with 29 (30 %) patients with CR and 44 (45 %) patients with PR. The best response was with the standardized regimen including IFNα, with 27 (93 %) with CR and 40 (91 %) with PR in addition to retinoids, with 24 (83 %) with CR and 38 (86 %) with PR. Thirty (41 %) patients died from their disease in the study [289].

Methotrexate Methotrexate had been studied in CTCL patients. Twenty-nine patients of median age 59 years (range, 13–85 years), with MF and SS who failed prior treatments underwent once-weekly oral, intramuscular, or subcutaneous methotrexate for 2–129 months. Overall response was 58 %, with 12 patients (41 %) who achieved CR and 5 (17 %) with PR. The median freedom from treatment failure was 31 months. Fourteen patients failed to respond, and median OS was 8.4 years [290]. A follow-up study in 69 patients with patch/plaque and tumor stage MF who received weekly oral or subcutaneous MTX included 60 of the 69 patients with stage T2 disease and with a median age of 67 years (range, 27–88 years) who had previously failed therapy. Seven (12 %) patients achieved CR and 13 (22 %)

achieved PR, with an overall response of 33 %; 36 (60 %) patients achieved stable disease, and 3 (5 %) experienced progressive disease. Median time to treatment failure with T2 disease was 15 months (95 % CI, 9–20 months). Adverse events included elevated aminotransferases, mucositis, and cutaneous erosion [291].

Liposomal doxorubicin Liposomal-encapsulated doxorubicin offer potential advantages over the corresponding unencapsulated agents. The liposome prolongs the half-life of the drug in the circulation and alters its bio-distribution pattern such that drug deposition is increased in tumor tissue and decreased in dose-limiting normal tissues. In one study, 44 CTCL patients with mean age of 65.4 years (range, 40–85 years) were treated with liposomal doxorubicin. Fifteen patients achieved a CR, 15 patients achieved a PR, 2 patients had SD, and 2 patients had PD during the first course. Median survival was 22.9 months in stage I–II CTCL compared to 14.6 months in stage III–IV disease. Adverse effects included hematological toxicity as well as capillary leak syndrome [292]. In another study, 25 patients with median age of 64 years (range, 32–77 years) with stage IIB–IV MF or SS were enrolled to receive liposomal doxorubicin. Fourteen (56 %) patients experienced an objective response, with 5 CRs and 9 PRs. The median PFS after the end of treatment was 5 months and the median OS was 45.8 months. Three (60 %) of the 5 patients who achieved CR relapsed. Adverse events included hematological toxicity, asthenia, GI upset, and palmoplantar erythrodysesthesia [293]. Finally, a third study enrolled 49 patients, mostly between 56 and 75 years of age, with refractory or recurrent stage IIB–IV MF to receive liposomal doxorubicin. The overall response rate was 40.8 %, similar to prior studies, with 3 (6.1 %) patients achieving CR and 17 (34.7 %) PR. Of the 20 responders, 14 experienced progression. Adverse events included hematological toxicity, allergy, pulmonary embolism, and cardiac ischemia [294].

Gemcitabine Gemcitabine is a cytosine nucleoside analogue exerting its action through ribonucleoside reductase inhibition and DNA chain termination. Gemcitabine has been studied in MF, and in one study, 33 patients with refractory/relapsed stage IB–IIA MF were analyzed. The overall response was 68 % (17/25 on the protocol), with 3 (12 %) CR. Four of the 8 patients who were treated with a lower dose of gemcitabine off protocol had a response, with 1 CR. Adverse events included myelosuppression, hemolytic uremic syndrome, heart failure, myocardial infection, transaminitis, rash, fever, and lethargy [295]. In another study, 32 patients with a median age of 58 years (range, 25–77 years), with untreated MF/SS and unspecified CTCL, underwent gemcitabine for six cycles. Overall response was 75 %, with 7 (22 %) achieving CR and 17 (53 %) PR. Of the

7 patients who achieved CR, 4 relapsed. The median PFS was 10 months and median OS was 19 months. Adverse events included hematological toxicity, hepatic toxicity, and alopecia [296]. Another study that included patients with MF and cutaneous PTCL enrolled 44 patients with a median age of 58 years (range, 25–82 years) also treated with gemcitabine. The overall response was 70.5 %, with 5 (11.5 %) patients achieving CR and 26 (59 %) patients achieving PR. The mean duration of CR was 15 months and that of PR was 10 months. Adverse events were similar to those in other studies [297].

Pentostatin (dCF; 2′-deoxycoformycin) Adenosine deaminase (ADA) is detectable in all mammalian tissues, with its activity greatest in the lymphoid system. Pentostatin is an inhibitor of adenosine deaminase, which converts adenosine to inosine in purine biosynthesis, found to be selectively toxic to lymphocytes. In one study, 37 patients of median age 58 years (range, 19–80 years) with refractory lymphoma or CTCL were treated with pentostatin; 31 patients were eligible for analysis. Overall response was 30 % with no one achieving CR and 4 (50 %) of the 8 CTCL patients achieving PR. The overall median survival for the study was 25.4 months. Adverse events included hematological, neurological, and ophthalmological toxicities, causing 3 patients to develop life-threatening infections [298]. In another study, 42 patients with median age 62 years (range, 38–86 years), with refractory or relapsed MF/SS or other CTCL underwent treatment with pentostatin; 10 (24 %) had various T-cell lymphomas and 32 (76 %) had MF/SS. The overall response rate was 54.8 %, with 5 (14.3 %) patients achieving CR and 17 (40.5 %) PR. The best outcomes were seen in patients with SS or PTCL. The median follow-up was 20 month,s and median duration of response was 4.3 months. Median failure-free survival was 2.1 months (range, 0.3–63 months), and adverse events included neutropenia, nausea, and CD4 suppression [299]. In one study, 8 patients with median age of 61 years (range, 31–81 years) with stage IIA–IV MF/SS were treated with pentostatin in addition to bexarotene and cyclophosphamide. The overall response was 87.5 %, with 5 (62.5 %) patients achieving CR. At last follow-up, 4 patients were alive with 3 in CR and 1 in PR; the remainder of the patients died of secondary neoplasia, disease progression, tumor lysis syndrome, or respiratory failure from prior chronic obstructive pulmonary disease (COPD). An adverse event was death from tumor lysis syndrome in the setting of high disease burden and previous renal failure [300].

Pralatrexate Pralatrexate was studied in 115 patients of median age 58 years (range, 21–85 years) with PTCL, including transformed MF (*n* = 12, 11 %). The ORR of the whole study was 29 % (95 % CI, 21–39 %), with 12 (11 %) CR, 20

(18 %) PR, and 21 (19 %) patients with stable disease. Of the patients with transformed MF, 3 (25 %) had a response. The median duration of response was 4.4 months, and median PFS was 5.3 months in the MF group. Median survival was 13 months. Adverse events included mucositis, elevated LFTs, bone marrow suppression, fatigue, herpes zoster, and rash [107, 301]. In another study, 54 patients with median age of 61.5 years (range, 30–81 years) with MF (stage ≥ IB), SS, or primary cutaneous ALCL were treated with pralatrexate. The MF group constituted the majority of the study with 38 (70 %) patients, the SS group had 15 (28 %) patients, and the primary cutaneous ALCL group had only 1 (2 %) patient. The overall response rate was 41 % (22/54; 95 % CI, 27.6–55.0 %), including 3 (5 %) CRs and 19 (35 %) PRs. The MF group had 1 (2.6 %) CR and 17 (44.7 %) PR. The SS group had 1 (6.7 %) CR and 2 (13.3 %) patients with PR. The ALCL patient went into CR. The median PFS was a little over a year. Adverse events included mucositis, fatigue, nausea, edema, epistaxis, pyrexia, anorexia, and skin toxicity [302].

Allogeneic stem cell transplant

No randomized control studies for stem cell transplant have been established for patients with advanced-stage CTCL [303]. However, one recent study enrolled 60 patients with median age of 46.5 years (range, 22–66 years) with advanced-stage MF ($n = 36$) and SS ($n = 24$), TNM stages IIB and higher, who underwent their first allogeneic stem cell transplant with 45 matched related and 15 matched unrelated donors. At last follow-up, 27 patients were alive, and 26 of them were in CR (43.3 %). The study showed a 5-year OS of 46 % (95 % CI, 35–61 %) and a PFS of 32 % (95 % CI, 22–47 %). Disease relapse/progression is the main cause of posttransplant failure, with a total of 27 patients (45 %) experiencing relapse/progression at a median of 3.8 months after HCT [304]. Another study enrolled 47 CTCL patients with median age at transplant of 51.5 years (range, 19–72 years) who underwent conditioning chemotherapy with or without antithymocyte globulin before allogeneic SCT. Twelve (25.5 %) patients enrolled had MF, 9 (19.1 %) had both MF and SS, and 26 (55.3 %) had large-cell transformation. At the time of report, 27 of the 47 were alive: 20 in CR, 1 in PR, 3 with stable disease, and 3 with progressive disease. Relapse after SCT was 50 %, and 5-year OS and PFS rates were 51 % and 26 %, respectively. Adverse effects included hematological suppression, infections, and graft-versus-host disease [305].

Novel treatments

Alemtuzumab (Campath-1H)

Alemtuzumab was studied in MF/SS patients where 22 patients with median age 61 years (range, 38–77 years) with CD52+ stage II–IV disease were enrolled. The study found an overall response of 55 % with CR in 7 (32 %) patients and PR in 5 (23 %) patients. Adverse events included fever, rigors, nausea, hypotension, rash, bronchospasm, fatigue, hematological toxicity, and infection [306]. In another study, 14 patients of median age 72 years (range, 48–82 years) with a diagnosis of SS received alemtuzumab. Twelve of the 14 (85.7 %) patients achieved a clinical response, with 3 (21.4 %) complete responses and 9 partial responses. At the end of the study, 7 of the 12 patients were still in remission. Median survival time was 35 months. Adverse events included erythema, edema, fever, headache, osteoarthralgia, and mild hematological toxicity [307]. Also, another study enrolled 39 patients with median age of 62 years (range, 20–83 years) with SS (23 patients) and advanced MF (16 patients) to be treated with alemtuzumab. The overall response rate was 51 % in the whole group, with 7 achieving CR and 13 PR; subgroup analysis revealed a 70 % response rate in patients with SS and a 25 % response rate in patients with MF ($p = 0.009$). The median time to progression was 3.4 months, although 6 patients (15 %) remained progression free for 56 months (median time). Adverse events included infections and hematological toxicity [308].

Brentuximab vedotin

Brentuximab vedotin was studied in CTCL, and in one study, 32 patients of median age 62 years (range, 20–87 years) with CD30+ (0–100 %) MF/SS who previously failed other therapy underwent treatment with brentuximab vedotin. The overall response was 70 %, seen in 21 of the 30 efficacy-evaluable patients (90 % CI, 53–83 %). One patient achieved CR and 20 patients achieved PR. PFS and event-free survival at 125 weeks were about 50 % and 20 %, respectively. Adverse events included peripheral neuropathy, fatigue, nausea, alopecia, and neutropenia [309]. In a phase II study, 48 patients with median age of 59.5 years (range, 31–77 years) with CD30+ lymphoproliferative disorders or MF were treated with brentuximab vedotin. The overall response was seen in 35 of 48 (73 %) patients with CR in 17 (35 %); specifically, the overall response was seen in 50 % of MF/SS compared to the overall response of 100 % in CD30+ lymphoproliferative disorders, although their responses were shorter in duration compared to MF. Median duration of response was 26 weeks, OS was 14.7 years (95 % CI, 10.2 years–not reached), and PFS was 1.1 years (95 % CI, 0.9–1.4 years). Adverse events included peripheral neuropathy, neutropenia, nausea, chest pain, DVT, and transaminitis [310].

Denileukin diftitox (DAB$_{389}$IL-2, Ontak)

Denileukin diftitox (DD) is a recombinant fusion protein consisting of the domains of the diphtheria toxin and human

interleukin (IL)-2. This gene, as expressed in *Escherichia coli*, results in the production of a single polypeptide chain that inhibits protein synthesis in cells that express the IL-2 receptor (IL-2R), resulting in cell death. Seventy-one patients with median age 61 years (range, 26–90 years) with refractory or recurrent stage Ib–IV CTCL underwent treatment with denileukin diftitox. The overall response was 30 %, with 7 patients (10 %) achieving CR; 50 of the 71 patients were non-responders, and adverse events included bone marrow suppression, sepsis, electrolyte imbalance, AKI, acute hypersensitivity events, chills, fever, nausea, vomiting, myalgia, GI complaints, vascular leak syndrome, and DVT [311]. Another study enrolled 144 patients with median age 59 years (range, 23–80 years) with pretreated stage I–III CTCL who underwent treatment with varying doses of denileukin diftiox. The ORR for the DD 18 μg/kg/day group was 49.1 %, with 5 of 55 (9.1 %) CR and 22 of 55 (40.0 %) PR compared with 15.9 % for the placebo group, with 1 of 44 (2.3 %) CR and 6 of 44 (13.6 %) PR ($p = 0.0015$). For the DD 9 μg/kg/day group, the ORR was 37.8 % with 5 of 45 (11.1 %) CR and 12 of 45 (26.7 %) PR ($p = 0.0297$), which suggested a dose response. Progression of disease was recorded in 52.3 % of the placebo patients but in only 21 % of all DD-treated patients. Estimated median PFS time was at least 971 days for the DD 18 μg/kg/day group, 794 days for the DD 9 μg/kg/day group, and 124 days for the placebo patients. Adverse events included capillary leak syndrome, nausea, vomiting, asthenia, and fevers and chills [312].

Mogamulizumab (KW-0761, Poteligeo)

In addition to targeting malignant T cells expressing CCR4, mogamulizumab may favorably influence the tumor microenvironment upon Treg depletion without causing autoimmune complications [313]. In one study, 41 patients with median age of 66 years (range, 35–85 years) with refractory or relapsed stage IB–IVB MF/SS were treated with mogamulizumab. The overall response evaluated in 38 patients was 36.8 %, with a higher rate in the SS (47.1 %) group compared to the MF (28.6 %) group. Three patients had CR and 11 patients had PR. Median PFS was 11.4 months, and the median duration of response was 10.4 months. Adverse effects included nausea, chills, infusion reaction, headache, pyrexia, and fatigue [314, 315]. A concurrent translational study found that 14 of 19 patients (73.7 %) had a reduction in CCR4 cells in the blood compared to 5 of 24 (20.8 %) in the skin. The difference between the responses in blood and in the skin may be attributed to the intravenous administration as well as higher numbers of CCR4 cells in blood compared to skin. A longer treatment time may be required to eliminate CCR4$^+$ cells from skin lesions [316]. Currently, a randomized phase III clinical trial studying patients with stage IB–IV MF/ SS comparing mogamulizumab and vorinostat in relapsed/ refractory CTCL is ongoing in the US (NCT01728805).

Conclusions

T-cell lymphomas are a rare and heterogeneous group of diseases with much still unknown. Treatment outcomes are poor, with high rates of relapse even when patients respond to upfront therapy. Even by understanding the etiology behind some of the T-cell lymphomas, treatment of the initial trigger of the tumorigenesis does not improve outcomes, as one would expect, as in ATLL and treatment of HTLV-1. Even as therapies are targeted toward specific gene mutations and expressions of subtypes of malignancy, there are high rates of division and mutation, resulting in relapse or refractory disease. Ongoing research about the biochemical, transcriptional, histopathological, and clinical progression of the disease is crucial to arm us with better treatment options so our patients can have better choices leading to improved overall survival. Clinical trials in T-cell lymphomas are often considered the first-line therapy because existing chemotherapy regimens are not as effective or as well tolerated by patients as we aspire, highlighting the importance of basic and clinical research in aiding us to defeat these types of lymphomas while minimizing adverse side effects of toxic regimens for our patients. With better understanding of the complex mechanisms involved, we look for a future when we can aim to achieve our utmost goal by curing patients with T-cell lymphomas.

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