Annals of Oncology 22 (Supplement 4): iv68–iv71, 2011
doi:10.1093/annonc/mdr260

XIV. T- and NK-cell lymphoproliferative disorders

S. Rosen, C. Querfeld, S. Kircher, B. Nelson, T. Kuzel, J. Guitart & A. Evens

Comprehensive Cancer Center of Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

Mature T-cell and natural killer (NK)-cell neoplasms (Table 1) represent a heterogeneous spectrum of post-thymic T-cell- and NK-cell-derived malignancies. They represent ∼12% of all non-Hodgkin lymphomas (NHLs). Significant geographic variation is noted with increased prevalence of select subtypes [i.e. adult T-cell leukemia/lymphoma (ATLL) and extranodal NK/T-cell lymphoma, nasal type] seen in Asian nations that may reflect exposure to etiologic agents such as human T-cell leukemia virus-1 (HTLV-1) and Epstein–Barr virus (EBV). The pathologic assessment of these cancers can be challenging and often requires immunophenotypic, cytogenetic and/or molecular analysis to ensure appropriate classification (Table 2). The most common entities will be discussed, highlighting clinical and pathologic manifestations, prognostic features and therapeutic strategies.

mycosis fungoides

Mycosis fungoides (MF) and its variants represent ∼50% of the cutaneous T-cell lymphomas (CTCLs) [1]. Its incidence in the USA is 2.8 per million individuals. The disease usually has indolent progression evolving from patch, plaque to tumor stage lesions. Five-year survival rates are ∼90%. Follicular MF tends to be more recalcitrant to treatment, has a greater propensity to transform and is associated with lower survival statistics.

Prognosis is dependent on TNMB stage, which reflects the extent and type of skin lesions. Nodal and visceral disease is typically a late clinical feature and associated with shortened survival. Treatment strategies acknowledge the skin-dominant manifestations of the disease and are often palliative, aimed at decreasing the tumor burden and improving cosmesis and maximizing comfort. Topical therapies include steroids, retinoids/rexinoids, nitrogen mustard, carmustine, narrow-band ultraviolet B (NB-UVB), psoralen plus ultraviolet A (PUVA), spot photon radiation and skin electron-beam radiation. Systemic therapies include interferon, retinoids/rexinoids (acitretin/bexarotene), histone deacetylase inhibitors (vorinostat/romidepsin), anti-folates (methotrexate/pralatrexate), denileukin diftitox (IL-2 receptor directed treatment), proteosome inhibitors (bortezomib), single-agent (e.g. gemcitabine, forodosine or doxil) or combination chemotherapy (e.g. CHOP or CMED). Topical and systemic treatments are often combined to speed and maximize response. Allogeneic stem cell transplantation is used in select instances and can provide prolonged disease control.

Sezary syndrome

Sezary syndrome is the aggressive leukemic variant of MF [2]. It represents <5% of the cutaneous lymphomas and has a 5-year survival rate of ∼25%. Clinical manifestations include exfoliative erythroderma, palmoplantar keratoderma, onychodystrophy, alopecia and ectropion. Patients are often disabled by the associated intense pruritus.

Therapeutic approaches are similar to MF, however, extracorporeal photophoresis and alemtuzumab (anti-CD52) appear to achieve higher response rates in this setting. Skin care including antibiotics, bleach baths and emollients can provide profound relief by decreasing *Staphylococcus aureus* colonization.

primary cutaneous CD30+ T-cell lymphoproliferative disorders (lymphomatoid papulosis and cutaneous anaplastic large cell lymphoma)

Primary cutaneous CD30+ T-cell lymphoproliferative disorders are the second most common group of cutaneous lymphomas [3]. The distinction between lymphomatoid papulosis and cutaneous anaplastic large cell lymphoma is often made on clinical grounds and can be challenging. The classic case of lymphomatoid papulosis is associated with recurrent papulonodular lesions that typically necrose, ulcerate and spontaneously involute. It is at times associated with MF and in a small percentage of patients with Hodgkin or NHL.

The majority of lesions have a clonally rearranged T-cell receptor. There are no definitive markers that distinguish the benign course of lymphomatoid papulosis (100% 5-year survival) from the progressive potentially life-threatening evolution to cutaneous anaplastic large cell lymphoma. Translocations involving the anaplastic lymphoma kinase (ALK) gene are not seen and ALK is not expressed in these tumors.

Lymphomatoid papulosis is managed by observation, intralesional steroid injections, topical bexarotene, UV therapy or low-dose methotrexate based on the extent of disease and frequency of recurrence. Spontaneous durable remissions have been witnessed following antibiotic treatment and pregnancy. Patients with progressive disease resembling frank lymphoma may be treated with spot radiation for isolated lesions or

Table 1. WHO classification of T-cell and NK-cell neoplasms (2008)

Mature T-cell and NK-cell neoplasms
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK+
Anaplastic large cell lymphoma, ALK–[a]
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Subcutaneous panniculitits-like T-cell lymphoma
Primary cutaneous CD8+ γδ T-cell lymphoma[a]
Systemic EBV+ T-cell lymphoproliferative diseases of childhood
Hydroa vacciniforme-like lymphoma
Aggressive NK-cell leukemia
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells[a]
Mycosis fungoides
Sezary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders[a]
Primary cutaneous CD4+ small/medium T-cell lymphoma

[a]Provisional entities for which the WHO Working Group felt there was insufficient evidence to recognize as distinct diseases at this time.

systemic chemotherapy for more advanced disease. Naked and conjugated monoclonal antibodies directed against CD30 have shown promising results in patients with progressive disease.

subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SCPTCL) is a rare clonal cytotoxic T-cell malignancy characterized by the appearance of subcutaneous nodules that often appear violaceous [4]. These lesions rarely become necrotic and ulcerate. Systemic symptoms are not uncommon and include weight loss, fever and fatigue. SCPTCL may be preceded by a benign-appearing panniculitis for years. Approximately 20% of patients have an associated autoimmune disease, most commonly systemic lupus erythematosus.

Recent data suggest a 5-year median survival exceeding 80% unless the hemophagocytic syndrome is present. Current management often includes local radiation, immunosuppressive agents (e.g. steroids, cyclosporine) and/or single-agent chemotherapy (e.g. methotrexate, chlorambucil). Combination chemotherapy is reserved for patients with aggressive and progressive variants.

primary cutaneous γδ T-cell lymphoma

Primary cutaneous γδ T-cell lymphoma is a rare hematologic malignancy presenting with disseminated cutaneous ulcerated plaques, nodules and/or tumors [5]. Mucosal involvement occurs but is uncommon. Systemic symptoms including weight loss, fevers and fatigue are almost universal.

The median survival is <2 years. Traditional combination chemotherapy results in short-term remissions. Allogeneic stem cell transplantation should be considered a component of initial treatment.

primary cutaneous CD8-positive aggressive epidermotrophic cytotoxic T-cell lymphoma

Primary cutaneous CD8-positive aggressive epidermotrophic cytotoxic T-cell lymphoma is currently a provisional entity in the WHO classification of mature T and NK neoplasms [6]. It is a rare disease accounting for <1% of CTCL. Most patients are adults and present with generalized papules, nodules, hyperkeratotic patches and/or plaques. Central ulceration and necrosis is common. Dissemination to other visceral sites frequently occurs including lung, testis, oral mucosa and the central nervous system usually sparing the lymph nodes.

An aggressive clinical course is typical with a median survival of <3 years. Combination chemotherapy rarely provides sustained remission. Antifolates can be effective in some patients. Allogeneic stem cell transplantation should be a consideration in medically fit patients.

peripheral T-cell lymphoma, not otherwise specified

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is the most common systemic mature T-cell lymphoma [7]. It comprises 5%–7% of NHL and ∼50%–60% of T-cell lymphomas in Western nations. The median age of diagnosis is ∼60 years with the majority of patients having advanced stage disease (75%) and International Prognostic Index (IPI) (score of 3–5) at presentation. Unfavorable characteristics include B symptoms (40%), elevated lactate dehydrogenase (LDH) (65%), bulky tumor >10 cm (10%), reduced performance status (30%) and extranodal disease (55%). Most common extranodal sites include bone marrow > liver > skin > lung and bone.

The prognosis is variable, related to IPI (or comparable T-cell associated prognostic index), and inferior to that seen with diffuse large B-cell lymphomas. Conventional-dose anthracycline-containing chemotherapy regimens produce overall response rates of ∼60% and 5-year overall survival of 20%–30%. The optimal regimen has not been defined. Autologous and allogeneic transplantation have controlled the disease in a minority of relapsed patients. Stem cell transplantation as part of the initial treatment strategy continues to be explored. Two new agents, pralatrexate (antifolate) and romidepsin (histone deacetylase inhibitor), have shown significant activity in patients with recurrent PTCL-NOS.

angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma (AILT) is a systemic disease with nodal involvement and associated disease features including B symptoms (50%–70%), skin rash, pruritus, pleural effusions, arthritis, eosinophilia and varied immunologic abnormalities (positive Coombs' test, cold agglutinins,

Table 2. Immunophenotype, EBV status and genetic features of peripheral T-cell NHL

Neoplasm	CD3; s, c	CD5	CD7	CD4	CD8	CD25	CD30	CD52	CD103	TCR	EBV	Genetic abnormality	T-receptor genes
Adult T-cell leukemia/ lymphoma	+	+	–	+	–	+	–/+	+	–	NA	–	Multiple	Rearranged
Peripheral T-cell lymphoma, NOS	+/–	+/–	+/–	+/–	–/+	NA	–/+	–/+	–	αβ>γδ	–	Often complex	Rearranged
Angioimmunoblastic T-cell lymphoma	+	+	+	+/–	–/+	NA	–[a]	–/+	–	αβ	Present in lymph nodes	Trisomy 3 and 5; additional X	Rearranged
Anaplastic large-cell lymphoma, primary systemic type (ALK+ and ALK–)	+/–	+/–	NA	–/+	–/+	+	+	–	–	αβ	–	Multiple, most common fusion gene is NPM-ALK	Rearranged
Subcutaneous panniculitis-like T-cell lymphoma	+	+	+	–	+	NA	–	NA	NA	αβ	–	–	Rearranged
Cutaneous γδ T-cell lymphomas	+	–	+/–	–	–	NA	–/+	NA	NA	γδ	–	–	Rearranged
Hepatosplenic γδ T-cell lymphoma	+	–	+	–	–	NA	–	NA	NA	γδ>αβ	–	i(7q) and trisomy 8	Rearranged
Extranodal NK/T-cell lymphoma, nasal type	–;+	–	–/+	–	–	NA	–	NA	NA	–	+	del 6 and 13	–
Enteropathy-type T-cell lymphoma	+	+	+	–	+/–	NA	+/–	NA	+/–	αβ>γδ	–	LOH 9p21	Rearranged

[a]T cells are CD30–; however, B cells are typically CD30+.

Abbreviations: LOH, loss of heterozygosity; del, deletion; I, isochrome; NA, not available, +, >90%, –, <90%, +/–, >50% positive, –/+, <50% negative; s, surface; c, cytoplasmic; NPM, nucleophosmin; ALK, anaplastic lymphoma kinase.

hemolytic anemia, antinuclear antibodies, rheumatoid factor, cryoglobulins and polyclonal hypergammaglobulinemia [8]. The median age of diagnosis is ∼60, it represents 3%–4% of all NHL and 15%–20% of T-cell malignancies. The majority of patients present with advanced disease.

Though spontaneous remissions have been noted, in most instances AILT follows an aggressive course with median survival of <2 years. Long-term remissions are uncommon with traditional combination chemotherapy. There are anecdotal reports of meaningful responses to lenalidomide and immunosuppressive agents (i.e. prednisone, cyclosporine, alemtuzumab). The role of auto and allogeneic stem cell transplantation remains to be defined though durable remissions have been seen with both modalities.

anaplastic large cell lymphoma

Anaplastic large cell lymphoma (ALCL) comprises two dominant subtypes based on the expression of the ALK protein [9]. These disorders represent 2%–3% of NHLs and ∼12% of T-cell lymphomas (equally divided between both entities). Nodal disease is common with 20% of patients having extranodal (skin, lung, liver, bone and bone marrow) involvement. However, involvement of the gastrointestinal tract and central nervous system is rare. ALK-positive patients are often children or young adults (median age third decade) with a slight male predominance, while ALK-negative patients are older (median age fifth decade). The majority of patients present with advanced stage disease.

Prognosis is associated with the patient's IPI score and age. The overall 5-year survival rate for ALK+ individuals treated with combination chemotherapy approaches 70% versus 50% for ALK– cases. Recent retrospective data suggest that the CHOEP regimen may be more effective than classic CHOP. Autologous stem cell transplantation can salvage patients with progressive disease but is usually reserved for ALK– and older individuals as part of the initial treatment strategy. Traditional and non-myeloablative allogeneic stem cell transplants may be curative. Vinblastine has significant single-agent activity in children. New agents with clear efficacy include pralatrexate and romedepsin. The expression of CD25 suggests a potential role for denileukin diftitox.

adult T-cell leukemia/lymphoma

ATLL is causally linked to the human T-cell virus type 1 (HTLV-1) [10]. HTLV-1 infection occurs through blood transfusions, sexual intercourse, shared needles, breast milk and vertical transmission. The overall risk of developing ATLL in HTLV-1 carriers is 2.5% by age 70 (median age 58). ATLL is endemic in southwestern Japan, the Caribbean basin and parts of central Africa. There are several clinical subtypes: (i) acute—leukemic picture, skin rash, generalized lymphadenopathy, hepatosplenomegaly, lytic bone lesions (hypercalcemia), CNS disease, elevated LDH and immunodeficiency; (ii) lymphoma—generalized lymphadenopathy without significant peripheral blood involvement, cutaneous rash, papules or nodules; (iii) chronic—circulating atypical lymphocytes, mild lymphadenopathy and exfoliative skin rash; and (iv) smoldering—circulating atypical lymphocytes, cutaneous lesions, without lymphadenopathy or hepatosplenomegaly.

Patients with the acute and lymphoma forms have median survival of <1 year, are typically treated with combination chemotherapy regimens (though durable responses with zidovudine plus interferon α have been seen in the acute form), and are candidates for allogeneic stem cell transplantation. Chronic-type patients have median survival of 2–5 years and responses have been witnessed with zidovudine plus interferon α. Smoldering patients can suvive for several years, may be observed and treated symptomatically, with ∼25% progressing to a more aggressive form. Treatment targeting CD25 and the chemokine receptor CCR4 continue to be explored.

extranodal NK/T-cell lymphoma, nasal and nasal-type

Extranodal NK/T-cell lymphoma, nasal and nasal-type is more prevalent in Asia and South and Central America [11]. The disease is associated with the EBV and most commonly seen in men with a median age in the mid-40s. Most patients have an extranodal presentation. These lymphomas have a predilection for the nasal cavity and paranasal sinues ('nasal') and typically present with stage I/II disease. The 'nasal type' designation is applied to other extranodal sites including skin, gastrointestinal tract, testis, kidney, upper respiratory tract and rarely orbit/eye—where more advanced disease with elevated LDH is often seen.

Combined modality therapy incorporating multi-agent chemotherapy plus radiation is most commonly used for nasal cavity and paranasal sinus presentations. Prognosis is based on extent of disease. Nasal-type presentations often have more extensive disease and disappointing long-term survival rates. L-Aparaginase has been shown to have significant activity against these malignancies and has been added to combination chemotherapy regimens being studied. The role of stem cell transplant for these malignancies continues to evolve.

enteropathy-associated T-cell lymphoma

Enteropathy-associated T-cell lymphoma (EATL) is a rare entity [12]. The classical type accounts for 80%–90% of presentations and is strongly associated with a history of previous celiac disease (HLA DQ2, DQ8 expression and anti-gliadin antibodies). Patients with the monomorphic type are less likely to have known celiac disease. Abdominal pain and weight loss is common. On endoscopy multiple ulcerating raised mucosal masses are usually seen. Bowel perforation is a known complication.

Historically EATL has been associated with a poor prognosis with few long-term survivors. Nutritional support is often essential. Though combination chemotherapy has been the standard, alternative strategies are necessary. The role of stem cell transplantation is being studied.

hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is an extremely rare disease, with a male predominance, affecting young adults [13]. Most patients present with systemic symptoms including fever and weight loss, prominent hepatosplenomegaly, lymphadenopathy and pancytopenia. Approximately 10%–20% of cases have a previous history of immune suppression or compromise.

HSTCL has the most dismal prognosis of all mature T-cell disorders with few long-term survivors. There is no acceptable standard chemotherapy regimen. Allogeneic stem cell transplant should be offered to all eligible patients.

references

1. Querfeld C, Rosen ST. Mycosis fungoides and Sézary syndrome. In O'Brien S, Vose JM, Kantarjian HM (eds), Management of Hematologic Malignancies. Cambridge, UK: Cambridge University Press 2009; 432–448.
2. Olsen EA, Rook AH, Zic J et al. Sézary syndrome: immunopathogenesis, literature review of therapeutic options, and recommendations for therapy by the United States Cutaneous Lymphoma Consortium (USCLC). J Am Acad Dermatol 2011; 64: 352–404.
3. Querfeld C, Khan I, Mahon B et al. Primary cutaneous and systemic anaplastic large cell lymphoma: clinicopathologic aspects and therapeutic options. Oncology 2010; 24: 574–587.
4. Willemze R, Jansen PM, Cerroni L et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: and EORTC Cutaneous Lymphoma Group study of 83 cases. Blood 2008; 111: 838–845.
5. Koch R, Jaffe ES, Mensing C et al. Cutaneous gamma/delta T-cell lymphoma. J Dtsch Dermatol Ges 2009; 7: 1065–1067.
6. Diwan H, Doina I. CD-8 positive mycosis fungoides and primary cutaneous aggressive epidermotropic CD-8 positive cytotoxic T-cell lymphoma. J Cutaneous Pathol 2009; 36: 390–392.
7. Escalon MP, Liu NS, Yang Y et al. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M.D. Anderson Cancer Center experience. Cancer 2005; 103: 2091–2098.
8. Mourad N, Mounier N, Briere J et al. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. Blood 2008; 111: 4463–4470.
9. Stein H, Foss HD, Durkop H et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000; 96: 3681–3695.
10. Tsukasaki K, Utsunomiya A, Fukuda H et al. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 2007; 25: 5458–5464.
11. Au WY, Weisenburger DD, Intragumtornchai T et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood 2009; 113: 3931–3937.
12. Cellier C, Delabesse E, Helmer C et al. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. Lancet 2000; 356: 203–208.
13. Belhadj K, Reyes F, Farcet JP et al. Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. Blood 2003; 102: 4261–4269.