Peripheral T-Cell Lymphoma, Not Otherwise Specified: Diagnosis and Therapeutic Approaches for the Advanced Practice Provider

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Abstract

T-cell lymphomas (TCLs) have a unique pathobiology, clinically aggressive course, and poor prognosis. Recently, there have been significant advances in understanding the molecular genetic alterations of TCLs through next-generation sequencing. This has led to the development of specific therapeutic molecules. This review aims to provide an up-to-date overview of the current therapeutic approaches for the subtype peripheral T-cell lymphoma, not otherwise specified.

Peripheral T-cell lymphomas (PTCLs) constitute a heterogeneous group of rare lymphoproliferative disorders that arise from post-thymic mature T cells or natural killer (NK) T cells (Luminari & Skrypets, 2021; Zain, 2019). The current World Health Organization (WHO) classification system recognizes approximately 30 subtypes of PTCLs, which are subdivided into nodal, extranodal, leukemic, and cutaneous PTCL (Table 1), each with multiple distinct disease entities that differ in morphology, immunohistochemical phenotype, gene expression profile (GEP), and clinical outcome (Hathuc & Kreisel, 2022; Luminari & Skrypets, 2021).

The most common distinct subtypes have a predominantly nodal presentation and include (1) PTCL, not otherwise specified (PTCL-NOS), which is the most prevalent group of PTCLs, accounting for 30% to 50% of all nodal PTCLs; (2) angioimmunoblastic T-cell lymphoma (AITL; 19%); and (3) anaplastic large cell lymphoma (ALCL), which can have the anaplastic lymphoma kinase (ALK) protein expressed (ALK+) or not (ALK–), accounting for approximately 12% of PTCLs (Oluwasanjo et al., 2019; Zhang & Zhang, 2020). Peripheral T-cell lymphoma subtypes

with extranodal presentation include (1) extranodal natural killer (NK), nasal type; (2) enteropathy-associated PTCL; (3) hepatosplenic PTCL; and (4) subcutaneous panniculitis accounting for 10%, 3%, 1%, and 0.9%, respectively (de Leval & Jaffe, 2020; Horwitz et al., 2022b).

EPIDEMIOLOGY, ETIOLOGY, AND CLINICAL PRESENTATION

According to the United States Surveillance, Epidemiology, and End Results (SEER) cancer registry, based on a 10-year period from 1997 to 2006, B-cell lymphomas (BCLs) vastly outnumber T- and NK-cell neoplasms at 27.96 per 1,000 persons compared with 2.09 per 1,000 persons, with PTCL incidence occurring in 0.5 to 2 per 100,000 people per year (Luminari & Skrypets, 2021). In western countries, PTCL accounts for 15% to 20% of all aggressive lymphomas and 10% of all non-Hodgkin lymphomas (NHL; Luminari & Skrypets, 2021; Zain, 2019). In contrast, the incidence is higher in Asia, where PTCL accounts for 20% to 25% of all aggressive lymphomas and approximately 20% of all NHLs (Zhang et al., 2018). The nodal subtypes of PTCL occur predominantly in patients from Europe and North America (Zing et al., 2018). The incidence of PTCL-NOS in the United States is highest among African Americans (Oluwasanjo et al., 2019). Most patients are adults with a median age of 60, and the diagnosis is more common in men than women, with a ratio of 2:1 (Zain & Hanona, 2021).

Table 1. Classification of Mature T- and NK-Cell Neoplasms According to the 2016 WHO Classification

Nodal • Peripheral T-cell lymphoma, NOS • Angioimmunoblastic T-cell lymphoma • Anaplastic large-cell lymphoma, ALK-positive • Anaplastic large-cell lymphoma, ALK-negative • Breast implant–associated anaplastic large-cell lymphoma • Follicular T-cell lymphoma • Nodal peripheral T-cell lymphoma with TFH phenotype
Extra-nodal • Extranodal NK, nasal type • Enteropathy associated • Hepatosplenic T-cell lymphoma • Subcutaneous panniculitis-like T-cell lymphoma
Leukemic • Aggressive NK cell leukemia • Chronic active EBV+ infection of T- and NK-cell type, systemic form • Adult T-cell leukemia/lymphoma • T-cell prolymphocytic leukemia
Primary cutaneous • Mycosis fungoides • Sézary syndrome • Primary cutaneous CD30+ T-cell lymphoproliferative disorders • Primary cutaneous gamma-delta T-cell lymphoma • Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma • Primary cutaneous acral CD8+ T-cell lymphoma • Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder

Note. WHO = World Health Organization; NOS = not otherwise specified; TFH = T follicular helper; NK = natural killer; EBV = Epstein-Barr virus. Information from Swerdlow et al. (2016).

Distinct risk factors associated with PTCL-NOS have not been identified. Similar to NHLs, PTCL is associated with exposure to various chemical substances, such as pesticides and fertilizers, tobacco smoking, exposure to infectious agents (Epstein-Barr virus [EBV], human T-cell lymphotropic virus 1 [HTLV-1]), psoriasis, and a history of celiac disease; Oluwasanjo et al., 2019). Epstein-Barr virus is found in approximately 30% of all cases of PTCL-NOS and may be associated with a more aggressive course (Nasr et al., 2019). Although obesity is not noted to be a significant risk factor for most NHL subtypes, a body mass index > 25 kg/m^2 had an increased risk factor and overall inferior survival with PTCL (Thandra et al., 2021).

PROGNOSTIC MODELS

The natural history and outcome of PTCL varies with histologic subtype. Except for ALCL, ALK+, most PTCLs are highly malignant and have an aggressive disease course with poor remission rate and frequent relapse after first treatment (Zain, 2019). Approximately 70% of patients are expected to relapse, with a median overall survival (OS) of 5.5 months after relapse (Luminari & Skrypets, 2021; Zhang et al., 2018).

Prognostic scores are central to discern patients likely to have a good outcome and those in need of intensive treatment. The International Prognostic Index (IPI), the Prognostic Index for T-cell lymphoma (PIT), the modified PIT (m-PIT), and the International peripheral T-cell lymphoma Project score (IPTCLP) are four

prognostic models used for PTCL-NOS (Table 2; Luminari & Skrypets, 2021).

The IPI, developed for BCL, has also been applied for the risk stratification of PTCL and correlates with OS when applied to PTCL. The scale assigns one point to each of the five potential risk factors of age greater than 60, Eastern Cooperative Oncology Group (ECOG) performance status greater than two, elevated serum lactate dehydrogenase (LDH), more than one extranodal site of involvement, and stage III or IV disease (Broccoli & Zinzani, 2017; Gutiérrez-García et al., 2011). A high score was associated with poorer outcome than in patients with lower scores when applied to PTCL. Patients with prognostic lower score (0–1) have a 5-year OS of 52% compared with 0% for those with higher score (4–5; Broccoli & Zinzani, 2017; Gutiérrez-García et al., 2011).

The Prognostic Index for T-cell lymphoma, like the IPI, aims for PTCL-specific prognostic indices and has been modified to m-PIT to better define clinical outcomes of PTCL-NOS. The m-PIT substitutes Ki-67 rather than bone marrow infiltration utilized in PIT (Broccoli & Zinzani, 2017).

The IPTCLP tool is used to prognosticate patients' OS (Oluwasanko et, al. 2019). It uses three variables and singles out four groups at different risk: group 1 (no adverse factors, with a 5-year OS of 58%); group 2 (one factor, with a 5-year OS of 15%); group 3 (two factors, with a 5-year OS of 5%); and group 4 (three or four factors, with a 5-year OS of 0%; Gutiérrez-García et al., 2011).

All four models incorporate a variety of clinical data for prognosis, including age, LDH, ECOG performance status, Ann Arbor stage of disease, presence of extranodal site, bone marrow involvement, thrombocytopenia, and Ki-67 index (Broccoli & Zinzani, 2017; Luminari & Skrypets, 2021).

Clinical prognostic factors associated with overall poor survival include advanced age (> 60), poor performance status (ECOG score > 2), elevated LDH, and bone marrow involvement (Zhang et al., 2018; Zing et al., 2018). In addition, GEP prognostic factors include the overexpression of GATA binding protein 3 (GATA3) or T-box transcription factor 21 (TBX21), which will be discussed in the pathobiology section. Subgroups characterized by high expression of GATA3 are associated with poor prognosis; conversely, high expression of

Table 2. Prognostic Models, Risk Score, and 5-Year Overall Survival

Variables	IPI	PIT	m-PIT	IPTCLP
Age (60 y)	y	y	y	y
ECOG (> 1)	y	y	y	y
LDH (elevated)	y	y	y	
Ann Arbor stage (III–IV)	y			
Extra-nodal involvement (≥ 2 sites)	y			
Bone marrow involvement		y		
Platelet count (< 150,000)				y
Ki-67 (≥ 80%)			y	
Prognostic risk score	Low: 0–1 Low-intermediate: 2 High-intermediate: 3 High: 4–5	Low: 0–1 Low-intermediate: 2 High-intermediate: 3 High: 3–4	Low: 0–1 Intermediate: 2 High: 3–4	Low: 0 Low-intermediate: 1 High-intermediate: 2 High: 3
5-year overall survival	Score 0-1: 52% Score 2: 25% Score 3: 20% Score 4–5: 0%	Score 0: 75% Score 1: 30% Score 2: 19% Score 3: 0%	Score 1: 39% Score 2: 0% Score 3–4: 0%	Score 0: 58% Score 1: 15% Score 2: 5% Score 4: 0%

Note. IPI = International Prognostic Index; PIT = Prognostic Index for T-cell lymphoma; m-PIT = modified PIT; IPTCLP = International peripheral T-cell lymphoma Project score; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase. Information from Gutiérrez-García et al. (2011); Horwitz et al. (2022b); Luminari & Skrypets (2021).

TBX21 is associated with a more favorable prognosis (Swerdlow et al., 2016).

The clinical presentation of PTCL-NOS is most often as disseminated disease (69%) with extranodal involvement (89%; Timmins et al., 2020). Common extranodal sites are the skin and gastrointestinal tract; however, the liver, spleen, lung, and bone marrow can also be involved (Broccoli & Zinzani, 2017). In addition, generalized lymphadenopathy and systemic B symptoms (fever, night sweats, weight loss) with occasional paraneoplastic features such as pruritus, eosinophilia, and hemophagocytosis are seen at presentation; while circulating lymphoma cells may be seen, leukemic presentation is uncommon (Siaghani et al., 2019). Common abnormal labs include anemia, thrombocytopenia, hypercalcemia, reactivation of cytomegalovirus and EBV, elevated serum LDH, and C-reactive protein (Oluwasanjo et al., 2019).

WORKUP

A multidisciplinary approach is crucial for the diagnosis and subclassification of these neoplasms. A combination of clinical assessment, immunophenotyping, morphology, molecular, and cytogenic analysis are essential to reach a conclusive diagnosis (Table 3). Immunophenotyping determines the antigen expressed on the cell surface and helps in distinguishing between B cell or T cell; the morphology assessment assists in determining cell size (small, medium, large); molecular profiling, along with cytogenic and fluorescence in situ hybridization (FISH), help to identify major translocations and T-cell receptor (TCR) gene rearrangement, providing further insight into different subtypes of PTCL (Swerdlow et al., 2016; Timmins et al., 2020).

The workup includes a comprehensive medical history and physical examination with attention to full skin, node-bearing areas including Waldeyer's ring, evaluation of the size of the liver and spleen, as well as evaluation of B symptoms, and performance status. Laboratory tests include a complete blood count with differential, comprehensive metabolic panel, measurement of serum uric acid, LDH, and serology studies for the detection of antibodies against human immunodeficiency virus (HIV type 1 and type 2) and HTLV type 1 and type 2. CT scans of the chest, abdomen, pelvis (CT CAP) with contrast is useful, both for establishing the diagnosis and staging the extent of lymphoma. Widespread or bulky adenopathy is more suggestive of lymphoma than carcinoma, infectious, or inflammatory conditions (Oluwasanjo et al., 2019). PET scanning is not generally helpful in making the diagnosis since inflammatory conditions and other cancers that present in a similar fashion to PTCL will often be fluorodeoxyglucose avid. PET can be useful as a baseline to assess disease burden, as well as during and immediately after treatment to assess response, although this remains to be validated (Nasr et al., 2019; Oluwasanjo et al., 2019). Finally, an excisional lymph node biopsy is preferred over a core needle biopsy for histology, flow cytometry, cytogenetics, and gene rearrangement studies. CD30 expression should be evaluated in all cases (National Comprehensive Cancer Network [NCCN], 2022; Zain, 2019). A bone marrow biopsy is recommended to confirm bone marrow involvement in patients with advanced-stage disease. Moreover, a multigated acquisition (MUGA) scan or echocardiogram is also recommended, since chemotherapy is usually anthracycline based (Horwitz et al., 2022b; NCCN, 2022).

PATHOBIOLOGY

The morphologic spectrum of PTCL-NOS is extremely broad. It is diagnosed on an exclusion basis as a disease whose features are not consistent with any of the other PTCL subtypes defined by the WHO classification, notably the exclusion of a T follicular helper (TFH) expression, although there is evidence that a subset of PTCL-NOS have TFH phenotype with pathological features of AITL (Broccoli & Zinzani, 2017; de Leval & Jaffe, 2020; Siaghani et al., 2019). The lymph node architecture of PTCL-NOS shows an inflammatory background composed of small lymphocytes, plasma cells, eosinophils, and histiocytes, and a diffuse effacement of lymphoid infiltrate composed of medium to large cells that have irregular hyperchromatic nuclei and a high proliferation rate (Figure 1; Hayashi et al., 2013; Siaghani et al., 2019; Swerdlow et al., 2008).

Peripheral T-cell lymphoma, not otherwise specified most commonly expresses CD4 (T helper phenotype) and much less commonly CD8

Table 3. Workup for Peripheral T-Cell Lymphoma, Not Otherwise Specified

Complete history and physical examination • Perform full skin exam, assess node-bearing areas, Waldeyer's ring, nasopharynx • Evaluate for organomegaly and B symptoms • Assess performance status • Calculate IPI/PIT • Pregnancy testing in patients of childbearing potential • Discussion of fertility issues and sperm banking
Blood test • Perform complete blood cell count with differential, LDH, complete metabolic panel, liver function test, uric acid, C-reactive protein • Test for HIV and human T-cell lymphotropic virus 1, hepatitis B and C testing • Consider quantitative EBV polymerase chain reaction
Radiologic test • Obtain PET/CT to assess for lymph node or visceral involvement • Echocardiogram or MUGA scan if anthracycline-based therapy is indicated
Biopsy (abnormal skin lesion and lymph node greater than 1.5 cm) • Check for immunologic markers: CD4+, CD3+, CD8+; CD4>CD8 expression; decreased or absent CD5, CD7; CD30+/– • Obtain flow cytometry for CD52+ • Evaluate for T-cell clonal rearrangement
Gene expression profile • Evaluate for *TBX21, GATA3*

Note. IPI = International Prognostic Index; PIT = Prognostic Index for T-cell lymphoma; LDH = lactate dehydrogenase; EBV = Epstein-Barr virus; MUGA = multigated acquisition. Information from NCCN (2022).

(cytotoxic phenotype). It is characterized by malignant cells expressing T-cell antigen CD3, CD2, CD5, and CD7, with frequent loss of CD5 and CD7 in up to 80% of cases (Al-Zahrani & Savage, 2017). Although CD4/CD8 double positive or negative is at times seen, a CD4+/CD8– phenotype predominates in nodal cases (Horwitz et al., 2022b). CD30 expression is variable and noted in 32% to 58% of cases. CD52 can be detected by flow cytometry in 35% to 100% of cases (Zain & Hanona, 2021). CD30 positivity often goes hand in hand with EBV cases (Nasr et al., 2019; Swerdlow et al., 2008). Aberrant expression of B-cell markers (CD20 and/or CD79a or CD15), scattered clear cells, and Reed-Sternberg–like cells can be seen. In addition, genetic features include TCR beta-chain expression and clonal T-cell receptor gene rearrangement (Table 4; Swerdlow et al., 2008).

Gene expression profiling has identified two major molecular subgroups of PTCL-NOS that are characterized by high expression of either *GATA3* or *TBX21* (Zain, 2019; Zain & Hanna, 2021). The first subgroup, *GATA3*, prominent in 33% of all PTCL-NOS, presents with more cytotoxic features, targets genes (*CCR4, Il18RA, CXCR7, IK*) that play a role in regulating T-helper 2 (TH2) cell differentiation, regulates interleukin-4 (IL-4), IL-5, and IL-13 expression, and exhibits mutation of genes (*CDKN2A/B-TP53* and *PTEN-PI3K*), while cooccurring gains/amplifications of STAT3 and MYC are noted (Amador et al., 2019; Timmins et al., 2020; Zain & Hanona, 2021).

The second subgroup, *TBX21*, prominent in 49% of PTCL-NOS, targets genes (*CXCR3, IL2RB, CCL3, INFγ*) that regulate T-helper 1 (TH1) cell differentiation and regulates the expression of interferon g (IFNg) 18 and granzyme B (Al-Zahrani & Savage, 2017; Amador et al., 2019). As stated previously, the *GATA3* subset carries a poorer prognosis compared with subset *TBX21*, with 5-year OS of 19% and 38%, respectively (Al-Zahrani & Savage, 2017; Zain & Hanona, 2021). Of note, a small subgroup of *TBX21*-expressing PTCL-NOS have a poor outcome due to expression of specific cytokine transcripts including CXCR3 and CXCL12, and were associated with CD8+ cytotoxic cells (Al-Zahrani & Savage, 2017; Amador et al., 2019).

Accurate diagnosis of PTCL can be challenging given the number of entities and rare nature of T-cell lymphomas. Often, multiple biopsies are necessary before a definitive diagnosis can be reached. Furthermore, a lack of agreement among pathologists has been described, given the similar morphological characteristics of all

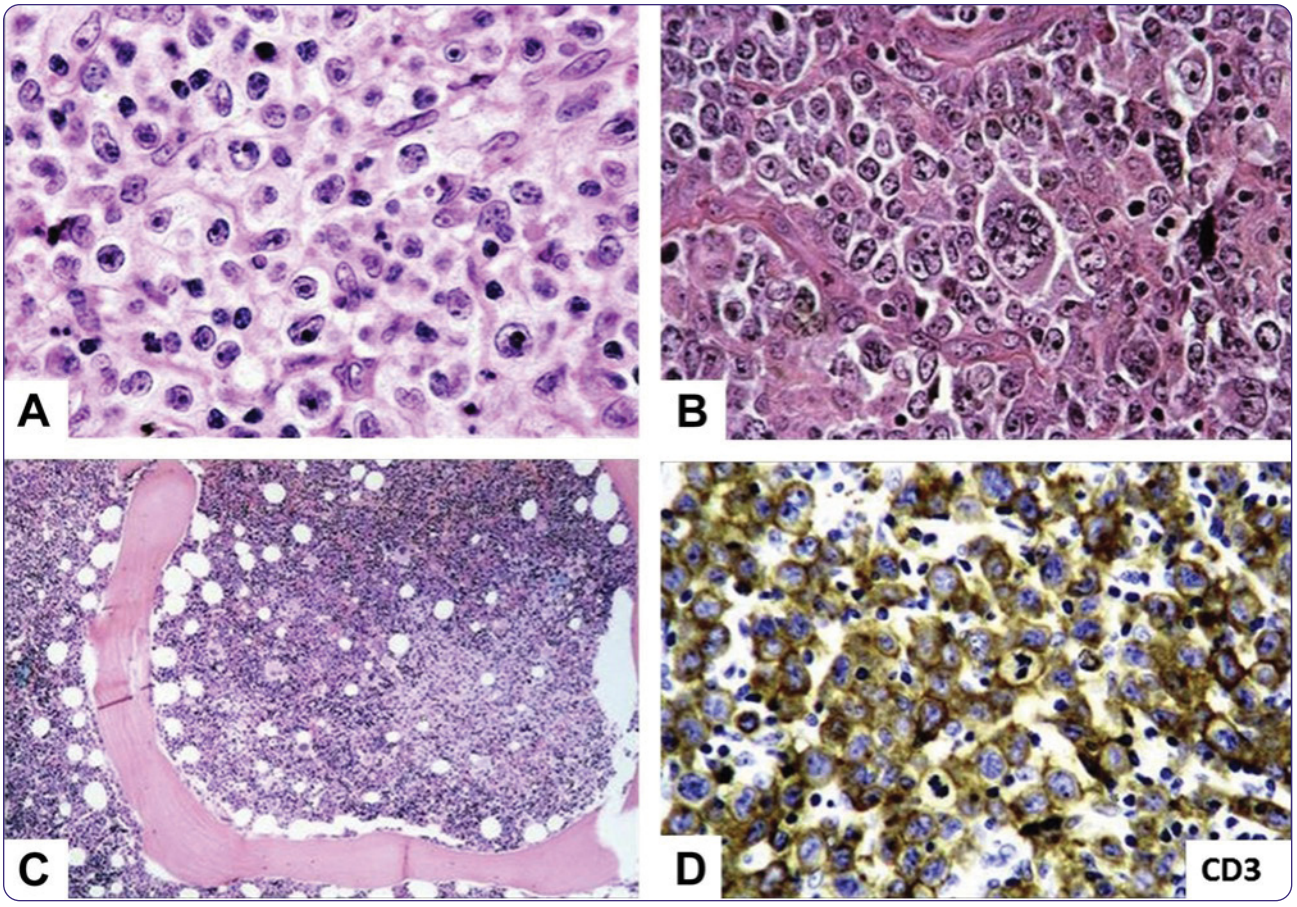

Figure 1. (A) Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) composed of pleomorphic medium to large cells with clear cytoplasm and nuclear irregularities; both mitotic figures and single-cell necrosis are noted. (B) PTCL-NOS composed of pleomorphic large cells with occasional giant cells, Reed-Sternberg–like cells with polylobated nuclei. (C) PTCL-NOS involving the bone marrow showing an ill-defined pleomorphic infiltrate with a non-paratrabecular localization associated with increased reticulin fibrosis and an admixed reactive inflammatory infiltrate. (D) The tumor cells are positive for CD3 with a predominant membranous pattern. Reproduced with permission from Al-Zahrani & Savage (2017).

subtypes (Oluwasanjo et al., 2019; Zain & Hanona, 2021).

The differential diagnosis to consider includes benign inflammatory infiltrate, BCLs, Hodgkin lymphoma (HL), and other PTCL subtypes, such as AITL and ALCL, ALK+/–, since they have similar morphologic and/or immunophenotypic features (Amador et al., 2022; Swerdlow et al., 2016).

The loss of expression of CD7 and/or CD5 is common and can help distinguish PTCL from a benign inflammatory infiltrate where both CD5 and CD7 are usually expressed (Nasr et al., 2019). Unlike PTCL-NOS, AITL tumor cells express CD10, BCL6, PD1, or CXL13 (Yabe et al., 2019). The hallmark of ALCL is large lymphoma cells with horseshoe-shaped nuclei and prominent nucleoli (Nasr et al., 2019). As Reed-Sternberg cells typically express CD15, CD30, and nuclear PAX5, and are CD45 negative, PTCL-NOS (CD30+) is differentiated from HL by the absence of PAX5, a B cell-specific factor seen in most cases of HL, and by the expression of alpha/beta TCRs (TCR beta positive) and other T-cell markers (Nasr et al., 2019).

FIRST-LINE TREATMENT

The standard therapeutic option for patients with stage III to IV disease is conventional-dose systemic anthracycline-containing chemotherapy. Patients who are eligible for anthracycline-based

Table 4. Clinicopathologic Features of Peripheral T-Cell Lymphoma Subtypes

Subtype	Immunophenotype	Genes involved
PTCL-NOS	CD4+, CD3+, CD8+, CD4>CD8 expression; decrease or absent CD5, CD7; CD30+/–; CD52+ by flow cytometry	*TBX21* (*CXCR3, IL2RB, CCL3, INFγ*) *GATA3* (*CCR4, IL18RA, CXCR7, IK*)
PTCL-NOS, nodal TFH	TFH cell origin (CD10+, CXCL 13+, PD1+, BCL6+, ICOS, SAP, CCR5)	
AITL	CD4+, TFH cell origin (CD10+, CXCL13+, PD1+, BCL6+, ICOS, SAP, CCR5), CD3+, CD4+, CD21+, CD23+, CD35+, CNA42+, EBV+ B cells, simulate HRS cells	*TET2, DNMT3A, RHOA, IDH2, CD28*
ALCL, ALK+	CD30+, ALK+, CD25+, CD43+	Rearrangement of the *ALK* gene t(2;5)(p23;q35)
ALCL, ALK–	CD30+, CD25+, CD43+	Rearrangements of *DUSP22* and *TP63*
cHL	TFH and positive for CD3, CD4, PD-1, CD57, and CD30 for majority of cases, CD15 (75%–85%), PAX5, and MUM1	

Note. PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified; TFH = T follicular helper; AITL = angioimmunoblastic T-cell lymphoma; HRS = Hodgkin/Reed-Sternberg; ALCL = anaplastic large cell lymphoma; cHL = classical Hodgkin lymphoma. Information from Nasr et al. (2019); Zain & Hanona (2021).

treatment are generally treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP; Zing et al., 2018). The 5-year OS with CHOP is 36%, overall response rate (ORR) 50%, and complete response rate (CRR) 20% to 30% (Broccoli & Zinzani, 2017; Oluwasanjo et al., 2019). Etoposide added to CHOP (CHOEP or dose-adjusted EPOCH) potentially benefits a subset of younger patients (age < 60 years) with normal LDH. In PTCL-NOS, AITL, and ALCL, ALK+, the addition of etoposide to CHOP improved the 3-year event-free survival (EFS) to 75% from 51% (Al-Zahrani & Savage, 2017; Horwitz et al., 2022a). However, aside from ALCL, ALK+, treatment responses are rarely durable and overall survival rate are similar (Horwitz et al., 2022b; Zain & Hanona, 2021). Data from the ECHELON-2 study demonstrated that the addition of brentuximab vedotin (Adcetris) to CHP (CHOP without vincristine) in PTCL-expressing CD30 significantly improved OS from 20.8 months to 48.2 months; however, with PTCL-NOS, brentuximab vedotin plus CHP did not improve outcomes compared with CHOP (Horwitz et al., 2019; Horwitz et al., 2022a). Studies investigating more intensive regimens have not demonstrated a significant improvement in OS (Oluwasanjo et al., 2019). The recommended induction therapy per NCCN Guidelines includes CHOP, CHOEP, EPOCH, brentuximab vedotin plus CHP (for CD30+ PTCL), and consolidation with high-dose chemotherapy with stem cell rescue (Horwitz et, al. 2016).

ROLE OF HEMATOPOIETIC CELL TRANSPLANT

Given the high relapse rate and poor outcome with PTCL, consideration should be given for hematopoietic cell transplant (HCT) in those patients whose disease is chemotherapy sensitive. Several retrospective and nonrandomized prospective studies have reported favorable outcomes in patients with PTCL who achieve complete remission (CR) and then proceed to HCT; however, interpretation of the studies is complex given the different histologic subtypes of PTCL and lack of subanalysis for PTCL-NOS (Horwitz et al., 2022b; Mehta-Shah, 2019). The Nordic Group conducted a prospective study evaluating 160 patients with PTCL (including 62 patients with PTCL-NOS) who underwent consolidative high-dose chemotherapy and autologous HCT. The 5-year OS for all PTCL and PTCL-NOS was 51% and 47%, respectively (Al-Zahrani & Savage, 2017). Although there are limited data, patients who have relapsed/refractory disease tend to benefit more from allogeneic HCT rather than autologous, and is a viable option over autologous HCT for young and fit patients (Oluwasanjo et al., 2019). In a randomized phase III study comparing autologous vs. allogeneic HCT, the OS and EFS were similar. The 3-year EFS after allogeneic HCT was 43% and for autologous HCT 38%; however, the allogeneic group resulted in significant transplant-related toxicity and mortality (31% vs. 0%), while the

autologous group had a higher incidence of relapse (36% vs. 0%; Horwitz et al., 2022b; Schmitz et al., 2021). Per NCCN Guidelines (2022), autologous stem cell transplant (ASCT) can be considered in patients with nodal aggressive PTCL who achieve a CR after primary therapy and are eligible based on age and comorbidity.

SECOND-LINE TREATMENT

There is no established standard therapy for relapsed/refractory disease. Second-line treatment recommendations for PTCL are defined based on eligibility for HCT and are further divided by T-cell lymphoma subtypes. The NCCN favors clinical trials; however, the same salvage combination regimens as for aggressive B lymphomas can be used, including DHAP (dexamethasone, cytarabine, cisplatin), ICE (ifosfamide, carboplatin, etoposide), GDP (gemcitabine, cisplatin, dexamethasone), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), or GemOx (gemcitabine, oxaliplatin; NCCN, 2022).

Apart from clinical trials, there are limited single-agent and combination regimens that are US Food and Drug Administration (FDA) approved for relapsed T-cell lymphoma (Table 5). Additionally, in the case of limited relapse (localized to one or two sites), involved site radiation therapy before or after ASCT may be an option (Horwitz et al., 2022b). Chemotherapy with single agents such as gemcitabine, etoposide, and alkylating agents have been used. Overall response rates up to 55% and CR rates of up to 30% in PTCL-NOS has been reported with the use of single-agent gemcitabine, which is often used in older, frail patients (Horwitz et al., 2022b; Oluwasanjo et al., 2019).

SINGLE AGENTS FOR RELAPSED PTCL

The histone deacetylase (HDAC) inhibitors romidepsin (Istodax) and belinostat (Beleodaq) were approved after two phase II studies revealed durable response in all PTCL subtypes (except for ALCL, ALK+, in the case of belinostat; Coiffier et al., 2012; Coiffier et al., 2014; O'Connor et al., 2015). Romidepsin received FDA approval in June 2011 based on a phase II study that evaluated 130 patients with relapsed/refractory PTCL and demonstrated highly durable responses in a subset of patients with relapsed/refractory PTCL, with responses ongoing at 48 months (Horwitz et al., 2022b). In PTCL-NOS, AITL, and ALCL, ALK–, the corresponding CR rates of 14%, 19%, and 19%, respectively and a median follow-up of 22 months showed no significant differences were seen in ORR or CR among the three subsets (Horwitz et al., 2022b). The most common adverse events (AEs) noted were ST-T wave changes, QTc prolongation, electrolyte imbalance, gastrointestinal upset, and cytopenias (Coiffier et al., 2012). Belinostat was FDA approved in July 2014 following the BELIEF study that established meaningful activity in relapsed/refractory PTCL. The ORR was higher for AITL, 45%, compared with PTCL-NOS, 23%, and ALCL, ALK–, 15% (Horwitz et al., 2022b; O'Connor et al., 2015). Common side effects included cytopenia and dyspnea (O'Connor et al., 2015).

Pralatrexate (Folotyn) received FDA approval in 2009 based on the pivotal, international phase II study PROPEL of heavily pretreated patients with relapsed or refractory PTCL. The ORR was lower in AITL at 8%, compared with PTCL-NOS and ALCL at 32% and 35%, respectively (Horwitz et al., 2022b; O'Connor et al., 2011). Pralatrexate is a folate antagonist and is a more potent analog of methotrexate with high affinity for the reduced folate carrier via which they both cross cell membranes (O'Connor et al., 2011). Common grade 3 AEs in pralatrexate include cytopenia and mucositis (O'Connor et al., 2011; Wudhikarn & Bennani, 2021).

Brentuximab vedotin is composed of an anti-CD30 monoclonal antibody conjugated to monomethyl aurostatin E (MMAE), a microtubule inhibitor (Horwitz et al., 2019; Pro et al., 2012). The antibody attaching to CD30 allows local release of MMAE in the tumor microenvironment, causing direct apoptotic cell death and inducing antibody-dependent cellular phagocytosis (Oluwasanjo et al., 2019; Pro et al., 2012). Brentuximab vedotin was first evaluated in patients with relapsed ALCL, where a high response rate of 86% was observed in patients who had failed prior therapies including stem cell transplant, with a CR of 57%. The median duration of response was 12.6 months with acceptable toxicity (Pro et al., 2012; Zain & Hanona, 2021). Brentuximab vedotin is approved for CD30+ PTCL. Given that up to 25% of PTCL-NOS patients express CD30 in

Table 5. FDA-Approved Therapies for Relapsed/Refractory Peripheral T-Cell Lymphomas

Drug	Class	Dose & Schedule	ORR/ CR, %	ORR PTCL-NOS, %	Side effects (≥ grade 3)
Romidepsin	Histone deacetylase inhibitor	14 mg/m² days 1, 8, and 15 of a 28-day treatment cycle	25/15	29	Thrombocytopenia (24%), neutropenia (20%), infections (all types, 19%)
Belinostat	Histone deacetylase inhibitor	1,000 mg/m² daily on days 1 to 5 every 21 days	26/11	23	Anemia (10.8%), thrombocytopenia (7%), dyspnea (6.2%), neutropenia (6.2%)
Pralatrexate	Antifolate	30 mg/m² once weekly for 6 weeks of a 7-week treatment cycle	29/11	32	Thrombocytopenia (32%), mucositis (22%), neutropenia (22%), anemia (18%)
Brentuximab vedotin	CD30-targeted antibody-drug conjugate	1.8 mg/kg (maximum dose: 180 mg) every 3 weeks	69/44	33	Neutropenia (21%), thrombocytopenia (14%), peripheral sensory neuropathy (12%)

Note. ORR = overall response rate; CR = complete response; PTCL-NOS = peripheral T-cell lymphoma, not otherwise specified. Information from Coiffier et al. (2012); Mehta-Shah (2019); O'Connor et al. (2015); Pro et al. (2012).

approximately 50% of tumor cells, brentuximab vedotin is recommend. The overall response rate in patients with PTCL-NOS has been reported at 20% to 33% (Mehta-Shah, 2019; Oluwasanjo et al., 2019). Other single-agent approaches, including alemtuzumab (Lemtrada), bortezomib (Velcade), gemcitabine (Gemzar), and lenalidomide (Revlimid), have only been studied in small, single-institution studies (Horwitz et al., 2022b).

Currently, there are several preclinical and clinical trials targeting specific proteins or receptors found in PTCL tumor cells, including CD5, CD7, CD25, CCR4, PI3K, mTOR, and JAK/STAT pathways (Toner et al., 2019; Zain & Hanona, 2021).

In addition, chimeric antigen receptor T-cell–based therapy and bispecific antibody therapy, which have generated much excitement in the BCL and myeloma world, are currently being explored in preclinical and clinical trial with multiple targets (Zain & Hanona, 2021).

SUPPORTIVE CARE

Myelosuppression

Chemotherapy-induced myelosuppression is associated with several systemic therapies, including CHOP, brentuximab vedotin, and pralatrexate. Patients' blood counts should be monitored regularly to assess the need for dose adjustment, treatment delay, or transfusion. Symptoms associated with anemia requiring intervention are sustained tachycardia, dizziness, hypotension, chest pain, and severe fatigue (Ow & Brant, 2021; Shelton, 2016). Neutropenia is characterized by a neutrophil count below 500 neutrophils/μL, or 1,000 neutrophils/μL with an expected further decline in 48 hours (NCCN, 2024). Patients should be aware of the risk for neutropenic fever, with a higher risk based on agent used, dose, age (older than age 65 years), performance status, bone marrow involvement, any open wound or skin infection, or any liver or kidney dysfunction. Advanced practice providers (APPs) should consider granulocyte–colony stimulating factor if one risk factor is identified (NCCN, 2024). Fever is defined as a single temperature of 38.3°C (101°F) or greater or a sustained temperature of 38°C (100.4°F) over 1 hour (NCCN, 2024).

Oral Mucositis

Oral mucositis is a potential complication in patients receiving systemic cytotoxic therapy, particularly pralatrexate. Severe mucositis affects the mucous membrane of the mouth and gastrointestinal tract, resulting in painful lesions that often limit food and fluid intake, require opioid analgesics, and increase the risk for infection because of the breach in the oral mucosa allowing entry of microorganisms (Brown, 2015). Mucositis can significantly affect quality of life and treatment outcomes and increase the chance for hospitalization and risk of death (Mercadante et al., 2015). It is imperative to identify treatment-related risk factors (e.g., use of pralatrexate) and patient-related risk factors (e.g., age > 65, poor nutrition,

immunosuppression, substance abuse). Counseling about oral side effects related to treatment and prevention strategies is important. Clinical assessment pre- and post-treatment is essential for the prevention and identification of complications. Current recommendations include oral care that focuses on consistent toothbrushing, flossing, and rinsing of oral cavities with alcohol-free bland oral rinse to remove debris, hydrate the oral cavity, and remove organisms (Brown, 2015; Ow & Brant, 2021). Patients should be educated to avoid irritating agents, including acidic, hot, or spicy foods, tobacco, and alcohol (Brown, 2015). For patients receiving pralatrexate, instruct patients to take folic acid at 1 mg by mouth daily and administer vitamin B12 every other month to reduce the risk of mucositis (Acrotech Biopharma, 2020).

Neuropathy

The risk for developing peripheral neuropathy increases with vincristine and brentuximab vedotin therapies. However, providers should consider other risk factors such as medical history of diabetes, alcohol overuse, vitamin B12 deficiency, and older age. Vincristine-induced peripheral neuropathy is characterized by sensory, motor, and autonomic signs and symptoms. Brentuximab vedotin neuropathy is manifest predominantly as sensory symptoms with patients reporting numbness (70%), paresthesia (70%), tingling (60%), and burning pain (40%; Merheb et al., 2022; Smith & Zanville, 2015). Although the most common manifestations of peripheral neuropathy are symptoms of numbness and tingling in the toes and fingers, peripheral neuropathy can affect any body part that is innervated by peripheral nerves and manifest with sensitivity to cold, burning, shooting, and electric shock–like sensations, muscle weakness, balance disturbance, constipation, urinary retention, sexual dysfunction, and blood pressure alteration (Merheb et al., 2022). Baseline and ongoing assessments will help patients and clinicians to keep alert of changes over time (Table 6). The physical exam should include gait, coordination, deep tendon reflexes, and sensation assessment. In addition, education and support is the key to maintaining patient safety. It is worth noting that patients with peripheral neuropathy are at increased rate for falls and a referral to physical therapy can lessen the risk (Smith & Zanville, 2015). Clinicians should consider that treatment-related peripheral neuropathy is a serious dose-limiting side effect that contributes to pain and debilitation. Although there is no standard prophylactic or therapeutic intervention to prevent or reduce peripheral neuropathy, several random control trials suggest that duloxetine has the most evidence of benefit (Merheb et al., 2022).

PRACTICE IMPLICATION

As with all cancer treatment, effective supportive care is essential. Advanced practice providers support patients and caregivers in understanding the disease trajectory. This is accomplished by providing thorough disease- and treatment-related education, including drug administration, schedule, common side effects, possible complications, and necessary precautions to take while on treatment. To accomplish this, APPs must understand the pathobiology of PTCL as it relates to diagnosis and prognostic features. Awareness of the differential diagnosis is crucial for early recognition and appropriate management. Second, APPs must be able to recognize high-risk clinical manifestations, as these assists with calculating prognostic scores and risk stratification. Third, APPs must be fully cognizant of the lines of treatments, including chemotherapy, immunotherapy, and targeted therapy and their side effects, which can be life-threatening. An important quality-of-life consideration is to ensure education for patients related to neuropathy and the potential for and consequences of neutropenia, including sepsis. Instruction on signs and symptoms of infection and what to do if patients experience any of these signs and symptoms is recommended. With education, patients' fear and anxiety diminishes, which enables them to tolerate treatment and AEs better. Education also provides a way for patients to feel empowered to manage their own health care.

CONCLUSION

Peripheral T-cell lymphomas are a heterogeneous group of rare neoplasms of mature T cells or NK cells with an aggressive course whose diagnosis continues to be clinically challenging. However, in recent years, significant progress has been made in the knowledge of the molecular pathogenesis

Table 6. History and Physical Exam Fundamentals

History examination • Details of chemotherapy regimen • Number of cycles, dose and cumulative dose • Onset of symptoms in relation to chemotherapy • Neuropathy occurring or worsening after chemotherapy cessation • Evidence of change over time (better or worse)
Symptoms • Distribution (hands, feet) • Sensory (numbness and tingling, paresthesia, neuropathic pain) • Motor (weakness, gait disturbance, difficulty with fine motor skills, foot drop) • Sympathetic (constipation, sexual dysfunction, blood pressure alteration) • Functionality and interference on activities
Sensation • Light touch • Pinprick or painful stimulus • Vibration sense • Cold/hot sensation
Other • Deep tendon reflexes • Motor function • Gait

Note. Information from Smith & Zanville (2015).

of PTCLs, which has led to the development of new agents. This has directed the shift from conventional cytotoxic approach to more specific molecular treatment, individualized approach, and hopefully, improved patient outcomes in the years to come. Given that the most important elements in the treatment of PTCL are early recognition and appropriate management, APPs, being at the forefront of health care, must understand this complex disease in order to diagnose, manage, and provide adequate patient education. ●

Disclosure

The authors have no conflicts of interest to disclose.

References

Acrotech Biopharma. (2020). Folotyn (pralatrexate) package insert. http://www.folotyn.com/wp-content/uploads/2019/11/Folotyn-PI-09-2020-REF-0255.pdf

Al-Zahrani, M., & Savage, K. J. (2017). Peripheral T-cell lymphoma, not otherwise specified: A review of current disease understanding and therapeutic approaches. *Hematology/Oncology Clinics of North America*, *31*(2), 189–207. https://doi.org/10.1016/j.hoc.2016.11.009

Amador, C., Bouska, A., Wright, G., Weisenburger, D. D., Feldman, A. L., Greiner, T. C.,...Iqbal, J. (2022). Gene expression signatures for the accurate diagnosis of peripheral t-cell lymphoma entities in the routine clinical practice. *Journal of Clinical Oncology, 40*(36), 4261–4275. https://doi.org/10.1200/JCO.21.02707

Amador, C., Greiner, T. C., Heavican, T. B., Smith, L. M., Galvis, K. T., Lone, W.,...Iqbal, J. (2019). Reproducing the molecular subclassification of peripheral T-cell lymphoma-NOS by immunohistochemistry. *Blood, 134*(24), 2159–2170. https://doi.org/10.1182/blood.2019000779

Broccoli, A., & Zinzani, P. L. (2017). Peripheral T-cell lymphoma, not otherwise specified. *Blood*, *129*(9), 1103–1112. https://doi.org/10.1182/blood-2016-08-692566

Brown, C. (2015). Mucositis. In C. G. Brown (Ed.), *A Guide to Oncology Symptom Management* (2nd ed., pp. 469-482). Pittsburgh, Pennsylvania: Oncology Nursing Society.

Coiffier, B., Pro, B., Prince, H. M., Foss, F., Sokol, L., Greenwood, M.,...Horwitz, S. (2012). Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *Journal of Clinical Oncology, 30*(6), 631–636. https://doi.org/10.1200/JCO.2011.37.4223

Coiffier, B., Pro, B., Prince, H. M., Foss, F., Sokol, L., Greenwood, M.,...Horwitz, S. (2014). Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. *Journal of Hematology & Oncology*, *7*, 11. https://doi.org/10.1186/1756-8722-7-11

de Leval, L., & Jaffe, E. S. (2020). Lymphoma classification. *Cancer Journal)*, *26*(3), 176–185. https://doi.org/10.1097/PPO.0000000000000451

Gutiérrez-García, G., García-Herrera, A., Cardesa, T., Martínez, A., Villamor, N., Ghita, G.,...López-Guillermo, A. (2011). Comparison of four prognostic scores in peripheral T-cell lymphoma. *Annals of Oncology*, *22*(2), 397–404. https://doi.org/10.1093/annonc/mdq359

Hathuc, V., & Kreisel, F. (2022). Genetic landscape of peripheral T-cell lymphoma. *Life (Basel), 12*(3). https://doi.org/10.3390/life12030410

Hayashi, E., Takata, K., Sato, Y., Tashiro, Y., Tachiyama, Y., Sawada-Kitamura, S.,...Yoshino, T. (2013). Distinct morphologic, phenotypic, and clinical-course characteristics of indolent peripheral T-cell lymphoma. *Human Pathology, 44*(9), 1927–1936. https://doi.org/10.1016/j.humpath.2013.03.002

Horwitz, S., O'Connor, O. A., Pro, B., Illidge, T., Fanale, M., Advani, R.,...Trümper, L. (2019). Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): A global, double-blind, randomised, phase 3 trial. *Lancet, 393*(10168), 229–240. https://doi.org/10.1016/s0140-6736(18)32984-2

Horwitz, S., O'Connor, O. A., Pro, B., Trümper, L., Iyer, S., Advani, R.,...Illidge, T. (2022a). The ECHELON-2 trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. *Annals of Oncology, 33*(3), 288–298. https://doi.org/10.1016/j.annonc.2021.12.002

Horwitz, S. M., Ansell, S., Ai, W. Z., Barnes, J., Barta, S. K., Brammer, J.,...Sundar, H. (2022b). T-Cell Lymphomas, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network, 20*(3), 285–308. https://doi.org/10.6004/jnccn.2022.0015

Luminari, S., & Skrypets, T. (2021). What's new in peripheral T-cell lymphomas. *Hematological Oncology, 39*(Suppl 1),

52–60. https://doi.org/10.1002/hon.2846
Mehta-Shah N. (2019). Emerging strategies in peripheral T-cell lymphoma. *Hematology. American Society of Hematology Education Program*, *2019*(1), 41–46. https://doi.org/10.1182/hematology.2019000012
Mercadante, S., Aielli, F., Adile, C., Ferrera, P., Valle, A., Fusco, F.,...Porzio, G. (2015). Prevalence of oral mucositis, dry mouth, and dysphagia in advanced cancer patients. *Supportive Care in Cancer*, *23*(11), 3249–3255. https://doi.org/10.1007/s00520-015-2720-y
Merheb, D., Dib, G., Zerdan, M. B., Nakib, C. E., Alame, S., & Assi, H. I. (2022). Drug-induced peripheral neuropathy: Diagnosis and management. *Current Cancer Drug Targets, 22*(1), 49–76. https://doi.org/10.2174/1568009621666210720142542
Nasr, M. R., Perry, A. M., & Skrabek, P. (2019). Peripheral T cell Lymphoma NOS. In D. Ivan (Ed.), *Lymph Node Pathology for Clinicians* (pp. 144): Springer.
National Comprehensive Cancer Network. (2022). T Cell Lymphomas. NCCN Evidence Block. https://www.nccn.org/professionals/physician_gls/pdf/t-cell_blocks.pdf
National Comprehensive Cancer Network. (2024). NCCN Clinical Practice Guidelines in Oncology: Hematopoietic growth factors. V.3 2024. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf
O'Connor, O. A., Horwitz, S., Masszi, T., Van Hoof, A., Brown, P., Doorduijn, J.,...Shustov, A. (2015). Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: Results of the pivotal phase II BELIEF (CLN-19) study. *Journal of Clinical Oncology, 33*(23), 2492–2499. https://doi.org/10.1200/jco.2014.59.2782
O'Connor, O. A., Pro, B., Pinter-Brown, L., Bartlett, N., Popplewell, L., Coiffier, B.,...Horwitz, S. (2011). Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study. *Journal of Clinical Oncology, 29*(9), 1182–1189. https://doi.org/10.1200/jco.2010.29.9024
Oluwasanjo, A., Kartan, S., Johnson, W., Alpdogan, O., Gru, A., Mishra, A.,...Porcu, P. (2019). Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). In S. Rosen, C. Querfeld, & J. Zain (Eds.), *T-Cell and NK-Cell Lymphomas: From Biology to Novel Therapies* (Vol. 176, pp. 83–98). https://doi.org/10.1007/978-3-319-99716-2_4
Ow, K. V., & Brant, J. M. (2021). Non-Hodgkin lymphoma: Examining mycosis fungoides and Sézary syndrome in the context of oncology nursing. *Clinical Journal of Oncology Nursing, 25*(5), 555–562. https://doi.org/10.1188/21.Cjon.555-562
Pro, B., Advani, R., Brice, P., Bartlett, N. L., Rosenblatt, J. D., Illidge, T.,...Shustov, A. (2012). Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: Results of a phase II study. *Journal of Clinical Oncology, 30*(18), 2190–2196. https://doi.org/10.1200/jco.2011.38.0402
Siaghani, P. J., Wong, J. T., Chan, J., Weisenburger, D. D., & Song, J. Y. (2019). Epidemiology and Pathology of T- and NK-Cell Lymphomas. *Cancer Treatment and Research, 176*, 1–29. https://doi.org/10.1007/978-3-319-99716-2_1
Schmitz, N., Truemper, L., Bouabdallah, K., Ziepert, M., Leclerc, M., Cartron, G.,...Tournilhac, O. (2021). A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL. *Blood, 137*(19), 2646–2656. https://doi.org/10.1182/blood.2020008825
Shelton, B. (2016). Myelosuppresion and second malignacies. In B. H. Gobel, S. Triest-Robertson, & W. H. Vogel (Eds.), *Advanced Oncology Nursing Certification Review and Resource Manual* (Second Edition) (2nd ed., pp. 451-490). Pittsburgh, Pennsylvania: Oncology Nursing Society.
Smith, E. M. L., & Zanville, N. (2015). Peripheral neuropathy. In C. G. Brown (Ed.), *A Guide to Oncology Symptom Management* (2nd ed., pp. 531-549). Pittsburgh, Pennsylvania: Oncology Nursing Society.
Swerdlow, S. H., Campo, E., Harris, N. L., Jaffe, E. S., Pileri, S. A., Stein, H.,...Vardiman, J. W. (2008). WHO classification of tumours of haematopoietic and lymphoid tissues (Vol. 2): International Agency for Research on Cancer, Lyon, France.
Swerdlow, S. H., Campo, E., Pileri, S. A., Harris, N. L., Stein, H., Siebert, R.,...Jaffe, E. S. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood, 127*(20), 2375–2390. https://doi.org/10.1182/blood-2016-01-643569
Thandra, K. C., Barsouk, A., Saginala, K., Padala, S. A., Barsouk, A., & Rawla, P. (2021). Epidemiology of non-Hodgkin's lymphoma. *Medical Sciences (Basel), 9*(1). https://doi.org/10.3390/medsci9010005
Timmins, M. A., Wagner, S. D., & Ahearne, M. J. (2020). The new biology of PTCL-NOS and AITL: Current status and future clinical impact. *British Journal of Haematology, 189*(1), 54–66. https://doi.org/10.1111/bjh.16428
Toner, K., Bollard, C. M., & Dave, H. (2019). T-cell therapies for T-cell lymphoma. *Cytotherapy, 21*(9), 935–942. https://doi.org/10.1016/j.jcyt.2019.04.058
Wudhikarn, K., & Bennani, N. N. (2021). How to sequence therapies in peripheral T cell lymphoma. *Current Treatment Options in Oncology, 22*(9), 74. https://doi.org/10.1007/s11864-021-00873-w
Yabe, M., Dogan, A., M, H. S., & Moskowitz, A. J. (2019). Angioimmunoblastic T cell lymphoma. In S. Rosen, C. Querfeld, & J. Zain (Eds.), *T-Cell and NK-Cell Lymphomas: From Biology to Novel Therapies* (Vol. 176). https://doi.org/10.1007/978-3-319-99716-2_4
Zain, J. M. (2019). Aggressive T-cell lymphomas: 2019 updates on diagnosis, risk stratification, and management. *American Journal of Hematology, 94*(8), 929–946. https://doi.org/10.1002/ajh.25513
Zain, J. M., & Hanona, P. (2021). Aggressive T-cell lymphomas: 2021 updates on diagnosis, risk stratification and management. *American Journal of Hematology, 96*(8), 1027–1046. https://doi.org/10.1002/ajh.26270
Zhang, J. Y., Briski, R., Devata, S., Kaminski, M. S., Phillips, T. J., Mayer, T. L.,...Wilcox, R. A. (2018). Survival following salvage therapy for primary refractory peripheral T-cell lymphomas (PTCL). *American Journal of Hematology, 93*(3), 394–400. https://doi.org/10.1002/ajh.24992
Zhang, P., & Zhang, M. (2020). Epigenetic alterations and advancement of treatment in peripheral T-cell lymphoma. *Clinical Epigenetics, 12*(1), 169. https://doi.org/10.1186/s13148-020-00962-x
Zing, N. P. C., Fischer, T., Zain, J., Federico, M., & Rosen, S. T. (2018). Peripheral T-cell lymphomas: Incorporating new developments in diagnostics, prognostication, and treatment into clinical practice-Part 1: PTCL-NOS, FTCL, AITL, ALCL. *Oncology (Williston Park), 32*(7), e74–e82.