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Clinical UPDATE

Diagnosis and Treatment of Non-Hodgkin T-Cell Lymphomas: Application of Biological Markers

FACULTY

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GOAL

The goal of this activity is to educate clinicians about the diagnosis and treatment of T-cell lymphomas, using updated research on drug pharmacology and pharmacokinetics, biological markers, and diagnostic tools.

INTENDED AUDIENCE

The intended audience for this activity comprises academic and community hematologists and oncologists, oncology nurses, oncology nurse practitioners, oncology physician assistants and associates, oncology pharmacists, and radiologists.

EDUCATIONAL OBJECTIVES

After completing this activity, participants should be better able to:

1. Recognize the epidemiology of T-cell lymphomas, including symptoms and risk factors.
2. Differentiate among T-cell lymphoma subtypes using biological markers.
3. Evaluate methods of biomarker detection for limitations and reliability.
4. Identify which quantity of a biomarker indicates positive expression.
5. Assess first- and second-line treatment options with emerging technologies for various subcategories of T-cell lymphoma.

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- MAC OS X 10.12, 10.13, and 10.14
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Diagnosis and Treatment of Non-Hodgkin T-Cell Lymphomas: Application of Biological Markers

Introduction

The term *lymphoma* refers to a collection of rare blood cancers that involve the uncontrolled growth of lymphocytes, or white blood cells. Non-Hodgkin lymphomas (NHLs) represent the most common hematologic malignancy worldwide and are responsible for approximately 3% of cancer diagnoses and deaths.[1] T-cell lymphomas are NHLs that develop from T lymphocytes, which are found in lymph tissue. These cancers involve tumor cells that are morphologically distinct from those found in other NHLs. Lymphomas can be nodal (originating in the lymph nodes) or extranodal (originating outside the lymph nodes)[2] and can form in organs, such as the spleen, tonsils, bone marrow, intestines, or skin.[3]

More than 40 types of T-cell lymphomas have been identified,[4] with incidence varying across countries and regions.[1,5] The most common is peripheral T-cell lymphoma (PTCL). It includes at least 30 subtypes[6] and accounts for 10% of NHL cases in the United States and Europe, 22% in South Korea, 25% in Japan, and 33% in China.[7] Survival rates also vary by subtype, but prognosis is poor for many subtypes,[8] and refractory disease is common.

Diagnosis of T-cell lymphomas can be difficult due to the rarity of these diseases and a lack of standardization in biomarker measurement. As technology has advanced, however, a general understanding of molecular analysis has increased. Methods of identifying biological markers of lymphomas currently include immunohistochemistry (IHC) and flow cytometry (FCM).[9] Several biological markers, including anaplastic lymphoma kinase (ALK) and CD30 positivity, are valuable for diagnosis, treatment, and prognosis.[4,6]

This educational activity reviews the diagnosis and management of T-cell lymphomas, including epidemiology, symptoms, and risk factors; the identification and measurement of biological markers; and established and emerging treatment options.

Epidemiology, Classification, and Key Subtypes

The 2 most updated classification proposals for lymphoid neoplasms are the International Consensus Classification[10] and World Health Organization Classification of Hematolymphoid Tumors 5th edition (WHO-HAEM5).[11] The WHO-HAEM5 includes additional categories, such as Epstein-Barr virus (EBV)-positive natural killer (NK)/T-cell lymphomas, hepatosplenic T-cell lymphoma, and primary cutaneous T-cell

Acronyms used in this activity

2L	Second-line
AE	Adverse event
AITL	Angioimmunoblastic T-cell lymphoma
AKI	Acute kidney injury
ALCL	Anaplastic large-cell lymphoma
ALK	Anaplastic lymphoma kinase
ARF	Acute renal failure
BIA-ALCL	Breast implant-associated anaplastic large cell lymphoma
BV	Brentuximab vedotin
BV-CHP	Brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisolone
CHEP	Cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisolone
CHP	Cyclophosphamide, doxorubicin, and prednisolone
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCL	Cutaneous T-cell lymphoma
DHAP	Dexamethasone, cytarabine, and platinum
DOR	Duration of response
DVT	Deep vein thrombosis
EATL	Enteropathy-associated T-cell lymphoma
EBV	Epstein-Barr virus
ED	Emergency department
ENKTL	Extranodal natural killer/T-cell lymphoma
ESHAP	Platinum (cisplatin or oxaliplatin), etoposide, methylprednisolone, and cytarabine
EZH1/2	Este homolog 1 and 2 enhancer
FCM	Flow cytometry
FDG-PET	F-fluorodeoxyglucose positron-emission tomography
GDP	Gemcitabine, dexamethasone, and cisplatin
GemOx	Gemcitabine and oxaliplatin
GVD	Gemcitabine, vinorelbine, and liposomal doxorubicin
HDACI	Histone deacetylase inhibitor
HSCT	Hematopoietic stem cell transplantation
ICE	Ifosfamide and carboplatin
ICOS	Inducible T-cell costimulatory
IHC	Immunohistochemistry
IPI	International Prognostic Index
ITK	Interleukin-2-inducible kinase
JAK	Janus kinase
LDH	Lactate dehydrogenase
LN	Lymph node tissue
MAHA	Microangiopathic hemolytic anemia
mDOR	Median duration of response
MF	Mycosis fungoides
MM	Multiple myeloma
MMAE	Monomethyl auristatin E
mOS	Median overall survival
mPFS	Median progression-free survival
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PD	Programmed death
PE	Pulmonary embolism
PET	Positron emission tomography
PFS	Progression-free survival
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma not otherwise specified
R/R	Relapsed or refractory
SDM	Shared decision making
STAT	Signal transducer and activator of transcription
SVC	Superior vena cava
TFH	T-follicular helper
TLS	Tumor lysis syndrome
WHO-HAEM5	World Health Organization Classification of Hematolymphoid Tumors 5th edition

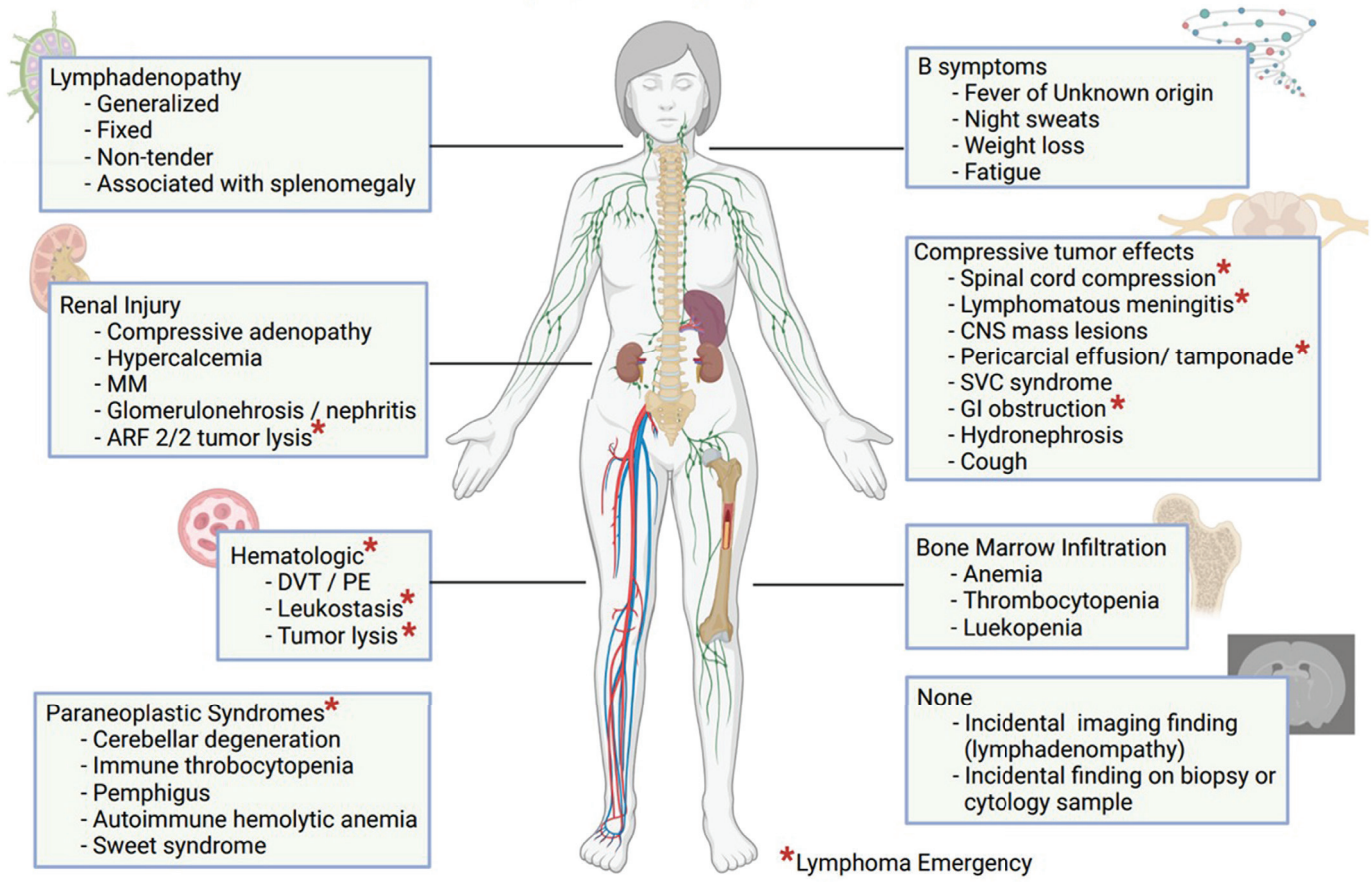

Figure 1. Key symptoms of lymphomas.[17]

ARF, acute renal failure; **CNS,** central nervous system; **DVT,** deep vein thrombosis; **GI,** gastrointestinal; **MM,** multiple myeloma; **PE,** pulmonary embolism; **SVC,** superior vena cava.

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lymphoma (CTCL). The exact names of the categories vary between the 2 sets of classifications, so they have been simplified for the purposes of this activity. In addition, precursor T-cell neoplasms, exclusively childhood cancers, and certain leukemias have been excluded, as they are outside the scope of this initiative.

The most common subtypes of T-cell NHLs in Western populations include peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), T-follicular helper (TFH) lymphomas, and anaplastic large-cell lymphoma (ALCL).

PTCL-NOS is the most common T-cell lymphoma. It accounts for 30% to 50% of T-cell lymphomas in the United States[6] and is more prevalent in men than women.[2] Onset typically occurs at around age 60, but it can also occur in younger adults and children.[2] PTCL-NOS is an aggressive cancer with a poor prognosis. Historical retrospective studies have demonstrated overall survival (OS) rates of 41% at 3 years and 32% at 5 years and progression-free survival (PFS) rates of 28% at 3 years and 23% at 5 years.[8]

ALCL accounts for 2% of all lymphomas and approximately 24% of all PTCLs in the United States.[12] ALCL is the most common type of T-cell lymphoma in children. Translocation of the ALK gene is a characteristic of a subgroup of ALCL called ALK-positive ALCL. This disease has a better outcome than ALK-negative ALCL, which lacks this translocation.[2,6,7]

TFH lymphomas are a group of lymphomas that arise from follicular helper T cells and include angioimmunoblastic T-cell lymphoma (AITL), follicular-type, and NOS. TFH lymphomas express at least 2 markers characterized by normal TFH cells (CD10, BCL6, CXCL13, programmed death [PD]1, and inducible T-cell costimulatory [ICOS]). These lymphomas also share genetic aberrations in epigenetic genes such as Tet2 and DNMT3 and as such are sensitive to epigenetic modulatory agents including histone deacetylase inhibitors (HDACIs) and demethylating agents.[13]

Risk Factors

A variety of risk factors for non-Hodgkin T-cell lymphomas have been identified; however, they tend to vary among subtypes. Some lymphomas are associated with previous infection with viruses such as HIV, EBV, and human herpesvirus 6.[14] The human T-lymphotropic virus, endemic in parts of Japan, the Caribbean basin, and the southern Mediterranean, is linked to adult T-cell leukemia/lymphoma.[2] Other risk factors include celiac sprue, which has been implicated in enteropathy-associated T-cell lymphomas (EATL),[2] and the use of immunosuppressive agents, which are often involved in the treatment of inflammatory bowel disease but have been linked to the development of hepatosplenic T-cell lymphomas. Most recently,

textured breast implants have been associated with ALCL of the capsule surrounding the implant, termed *breast implant-associated anaplastic large cell lymphoma* (BIA-ALCL).[15] A genetic component has also been suggested in NHLs, as a family history of lymphoma may be a risk factor. These genetic risks have not been well characterized. Finally, environmental exposures to chemicals and pesticides such as dioxin have also been associated with the development of lymphomas.[14]

Presentation and Diagnosis

Symptoms associated with T-cell lymphomas vary widely among subtypes but include swollen lymph nodes, anemia, thrombocytopenia, and liver or spleen enlargement (**Figure 1**).[17] So-called Category B symptoms consist of fever, unexplained weight loss, and night sweats. Skin rashes and/or itching can occur and are characteristic of the cutaneous lymphomas such as mycosis fungoides and Sezary syndrome.[2] Patients also may be asymptomatic at presentation or exhibit atypical symptoms, often secondary to organ involvement or bone marrow infiltration.[17]

Other patients may require immediate medical attention for a range of oncologic emergencies. For example, an enlarged tumor can cause vena cava syndrome, malignant epidural spinal cord compression, malignant pericardial effusion, or gastrointestinal obstruction.[18] Paraneoplastic syndromes associated with cytokine release and hemophagocytic lymphohistiocytosis can occur and may require emergency treatment of the underlying lymphoma.[17]

Individuals with Category B symptoms should undergo a comprehensive lymph node exam. In the case of lymphadenopathy or splenomegaly, a further workup for lymphoma is warranted, regardless of patient age. When assessing probable lymphoma in general practice, routine laboratory studies are often helpful in identifying cytopenias, elevated lymphocyte counts due to circulating tumor cells, or metabolic abnormalities associated with hepatic involvement or organ injury (**Table 1**).[17] Once the suspicion of lymphoma has been established, a multidisciplinary approach to diagnosis often involves collaboration among specialists in radiology, cytomorphology, immunophenotyping, hematopathology, oncology, and nursing.[19]

Positron emission tomography (PET) scanning is used to identify the location and staging of the most enlarged nodes for biopsy.[14] 18F-fluorodeoxyglucose PET (FDG-PET) is a standard imaging modality for staging because the extranodal spread of T-cell lymphomas may not be captured by other imaging methods. This renders PET scans as a key instrument in the early detection of NHLs.[20] However, PET scans can only detect lymphomas that are avid for 18F-FDG, and PTCLs vary widely in their degree of FDG avidity. For example, nodal lymphomas frequently have an increased FDG uptake and CTCLs, such as mycosis fungoides and Sezary syndrome, typically have low to moderate FDG uptake.[21]

T-cell lymphomas are typically diagnosed through lymph node biopsy. Open surgical biopsy is the gold standard; however, physicians often use core needle biopsy or nodal excision.[14] Fine-needle biopsies should not be done for diagnosis of lymphomas as they do not accurately reflect the underlying architecture or provide adequate sampling for diagnosis. IHC, FCM, and molecular studies should be performed on tissue from the biopsy to confirm diagnosis and subtype.[9]

The essential panels for T-/NK-cell lymphoma

Table 1. Laboratory testing for probable lymphoma in general practice.[17]

Laboratory test	Rationale	Abnormalities suggestive of lymphoma	Red flag results
Complete blood count	Ensure trilineage normality, assess for gross abnormalities suggestive of bone marrow involvement	Anemia, thrombocytopenia, leukopenia/leukocytosis	Neutropenia, WBC >100 K, severe anemia, or thrombocytopenia
Comprehensive metabolic panel	Assess for the presence of hepatic or renal dysfunction suggestive of compressive or infiltrative disease	AKI, electrolyte abnormalities, hepatic or cholestatic injury patterns	Significant electrolyte abnormalities or evidence of significant organ injury
Phosphorus	Evaluate for evidence of tumor lysis. (Although phosphate levels in spontaneous TLS may be normal as opposed to phosphate levels in post-chemotherapy TLS)	Tumor lysis	Hyperphosphatemia with phosphorus levels >4.5 mg/dL in adults or >25% increase from baseline (in conjunction with elevated LDH, uric acid, potassium, ± AKI, as this is consistent with TLS)
LDH	Evaluate for evidence of rapid cellular turnover, which may be associated with TLS	Elevated LDH	In conjunction with elevated potassium, uric acid ± AKI, and hyperphosphatemia as this is consistent with TLS
Uric acid	To rule out TLS	No clear association outside of TLS	Hyperuricemia with uric acid >8 mg/dL or 25% increase from baseline In conjunction with elevated LDH, potassium, ±AKI, and elevated phosphorus, as this is consistent with TLS

AKI, acute kidney injury; **ED,** emergency department; **LDH,** lactate dehydrogenase; **MAHA,** microangiopathic hemolytic anemia; **TLS,** tumor lysis syndrome.

Table 2. Summary of reported CD30 expression rates in patients with PTCL and CTCL.[7,29-38]

Reference	Method	CD30 antibody	CD30+ cell cutoff, %	PTCL-NOS, %	AITL, %	ATLL, %	ENKTL, %	ALK– ALCL, %	ALK+ ALCL, %	EATL, %	CTCL/ MF, %
Karube et al, 2008[29] (N=319)	FCM	NR	>70	5	0	15	0	58[a]		–	9/–
			20-70	11	32	24	64	35[a]		–	9/–
Savage et al, 2008[30] (N=490)	IHC	NR	>0	32	–	–	–	100	100	–	–
			≥80	5	–	–	–	–	–	–	–
Asano et al, 2011[31] (N=47)	IHC	Ber-H2	>30	51[b]	–	–	–	–	–	–	–
Duvic 2011[32] (N=106)	IHC	NR	>10	–	–	–	–	–	–	–	–/11[c]
Weisenburger et al, 2011[33] (N=217)	IHC	NR	>20	32	–	–	–	–	–	–	–
Sabattini et al, 2013[34] (N=192)	IHC	Ber-H2	0: no staining	36	51	–	20	–	–	0	–/41
			1+: >0 to <25	13	21	–	10	–	–	0	–/47
			2+: 25–50	21	12	–	30	–	–	22	–/6
			3+: >50–75	13	10	–	10	–	–	0	–/0
			4+: >75	18	0	–	30	–	–	78	–/6
Bossard et al, 2014[35] (N=376)	IHC	Ber-H2	0: <5	42	37	44	54	0	0	50	–
			1+: 5–24	26	47	11	7	0	0	0	
			2+: 25–49	9	10	33	11	0	5	0	
			3+: 50–75	10	5	11	14	0	2	7	–
			4+: >75	13	0	0	14	100	93	43	
Lamarque et al, 2016[36] (N=46)[d]	IHC	NR	<5	10	0	100		0	0	0	14/–
			5–24	10	100	0	–	0	0	100	0/–
			25–49	30	0	0	–	0	20	0	0/–
			50–75	30	0	0	–	0	20	0	14/–
			>75	20	0	0	–	100	60	0	71/–
Wang et al, 2017[37] (N=122)	IHC	NR	0: no staining	–	–	–	30	–	–	–	–
			1+: >0 to <25	–	–	–	38	–	–	–	–
			2+: 25–50	–	–	–	18	–	–	–	–
			3+: >50–75	–	–	–	10	–	–	–	–
			4+: >75	–	–	–	5	–	–	–	–
Kawamoto et al, 2018[38] (N=97)	FCM and IHC	Ber-H2	≥1	–	–	–	57	–	–	–	–
			≥10	–	–	–	55	–	–	–	–
			≥20	–	–	–	44	–	–	–	–

AITL, angioimmunoblastic T-cell lymphoma; **ALCL,** anaplastic large-cell lymphoma; **ALK,** anaplastic lymphoma kinase; **ATLL,** adult T-cell leukemia/lymphoma; **CTCL,** cutaneous T-cell lymphoma; **EATL,** enteropathy-associated T-cell lymphoma; **ENKTL,** extranodal natural killer/T-cell lymphoma; **FCM,** flow cytometry; **IHC,** immunohistochemistry; **LN,** lymph node tissue; **MF,** mycosis fungoides; **NR,** not reported; **PTCL-NOS,** peripheral T-cell lymphoma not otherwise specified.

[a] Data are for any ALCL regardless of ALK-positive status.

[b] Cytotoxic molecule-positive PTCL-NOS.

[c] Data are for 10 of 42 patients with late-stage MF and 2 of 64 with early-stage MF.

[d] Retrospective study of patients who previously underwent CD30 testing and were treated with CD30-directed therapy.

diagnosis include T- and B-cell markers, Ki-67, and EBV in situ hybridization. The National Comprehensive Cancer Network (NCCN) guidelines list several recommended panels for diagnosis and accurate subtyping of T-cell lymphomas, including CD4, CD8, CD56, CD30, ALK, TIA-1, granzyme B, PD-1, CXCL13, CD10, Bcl-6, ICOS, CD2, CD5, CD7, CD21, -F1, and TCR-delta.[22,23] One limitation of IHC is the high variability in evaluation of IHC markers.[24] Discrepancies in the degree of staining can make confirming a diagnosis difficult in some cases.

FCM can be helpful in detecting CD30 expression due to its sensitivity.[25] A combination of IHC and FCM is best practice for consistent detection, although FCM is generally used as an adjunct test.[9] Physicians may also consider the use of open-source software for digital pathology image analysis to streamline quantitative assessment.[24]

Biological Markers

Several biomarkers that may have prognostic or diagnostic importance in T-cell lymphomas include ALK, CD30, GATA3, TBX21, and RHOA G17V. The degree of staining for each biomarker varies by subtype and affects diagnosis, treatment, and prognosis.[24]

ALK is a protein that is expressed on surface of cells. Overexpression of ALK protein, or ALK positivity, is often demonstrated in ALCL.[26] ALK-positive ALCL has an overall favorable outcome with certain chemotherapy combinations, such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone)-type regimens.[27] ALK-negative ALCL, however, is associated with worse outcomes and requires more aggressive treatment. This may include stem cell transplantation as consolidation in first remission.[6]

AITL is associated with mutations in epigenetic genes such as TET2, RHOA, and IDH2. The **RHOA G17V** mutated subtype of AITL is associated with Category B symptoms, stronger PD-1 expression, and poor outcomes.[28] In patients with PTCL-NOS, **GATA3** gene expression is associated with poorer prognosis, and **TBX21** cases have better outcomes.[8]

CD30 is a protein and receptor of the tumor necrosis factor family that is expressed in a subset of T-cell lymphomas.[7] CD30 is highly expressed in both ALK-positive and ALK-negative ALCL, including BIA-ALCL.[7,15] CD30 expression has also been found by IHC in 32% to 64% of PTCL-NOS cases, 50% to 100% of EATL cases, and 46% to 80% of AITL cases. Due to a lack of standardization, the cutoff percentage for CD30 positivity varies among studies and clinical trials, and in clinical practice. In a recent literature review, included studies used a wide range of cutoffs for CD30 positivity, from >10% to >80%. More recent studies use a 5-tiered scale with categories of <5%, 5% to 24%, 25% to 49%, 50% to 75%, and >75% (**Table 2**).[7,29-38]

Current Treatment Options for PTCL-NOS, ALCL, and TFH Lymphomas

CHOP-based regimens have typically been associated with high response rates but primary treatment failure in up to 40% of patients with PTCL and 5-year OS rates of only 35%.[39] Responses to CHOP alone have not been durable, thus the recommendation for consolidation with autologous stem cell transplantation in responders.[39,40] Therefore, many efforts have been made to improve this regimen. For the purpose of this review, discussion of treatment strategies will focus on the 3 most common forms of T-cell lymphoma: PTCL-NOS, ALCL, and TFH lymphomas.

Chemotherapy Combinations

BV-CHP, a combination of brentuximab vedotin (BV), cyclophosphamide, doxorubicin, and prednisolone (CHP), is now approved as a first-line treatment for ALCL, which commonly expresses CD30.[7,41] BV consists of a human chimeric immunoglobulin G1 antibody directed against CD30 that is covalently linked to the potent microtubule-disrupting agent, monomethyl auristatin E (MMAE) by a protease-cleavable linker.[42,43] The binding of BV to CD30 on the tumor cell membrane triggers a cascade of events that ultimately results in apoptotic death of the CD30-expressing tumor cell (**Figure 2**).[43]

In addition to its direct anti-tumor activity related to the apoptosis of CD30+ tumor cells, BV may also exert anti-tumor activity via other indirect mechanisms, based on in vitro and in vivo studies.[44] Because MMAE crosses the cell membrane and is released into the surrounding extracellular matrix, BV also potentially exerts cytotoxic activity on "bystander" tumor cells, irrespective of CD30 status. This may explain its activity in heterogeneous tumors such as Hodgkin lymphoma.

The ECHELON-2 study was a multicenter, randomized, phase 3 study that compared frontline therapy with CHOP vs CHOP plus

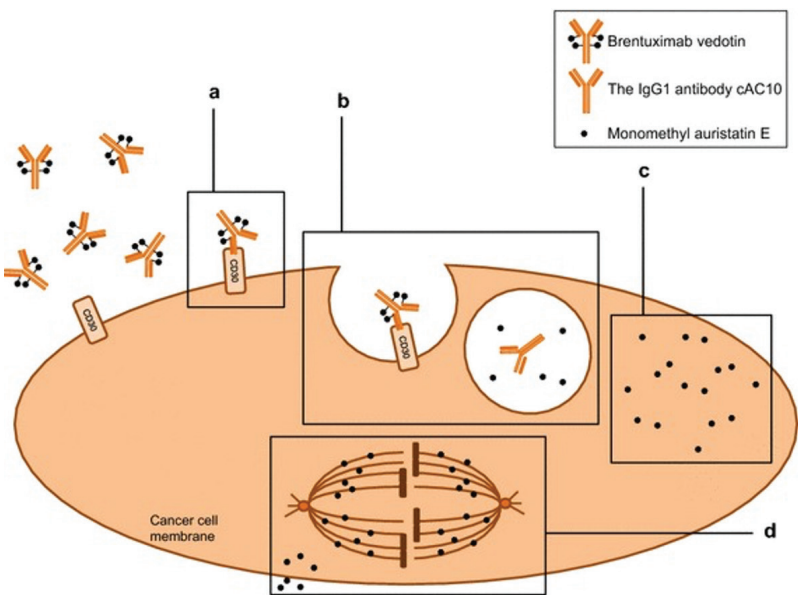

Figure 2. Mechanism of action of BV in a CD30+ tumor cell.[43]

a) BV binds to the CD30 membrane receptor. **b)** The CD30–drug complex is internalized and traffics to a lysosome, where enzymes cleave the linker between the antibody and MMAE, a microtubule-disrupting agent. **c)** MMAE is released intracellularly, where it: **d)** binds to tubulin (leading to G2/M cell cycle arrest and concurrent induction of apoptosis), and extracellularly into the surrounding area, where MMAE may induce apoptosis in surrounding cells (bystander effect), irrespective of CD30 status.

BV, brentuximab vedotin; **MMAE,** monomethyl auristatin E.

Used with permission from Scott LJ. Brentuximab vedotin: a review in CD30-positive Hodgkin lymphoma. *Drugs*. 2017;77(4):435-445. Springer Nature.

BV for CD30-positive PTCLs.[45] Vincristine was dropped from the BV-CHP arm of the study due to avoid overlapping neurotoxicity with BV. The study was enriched for patients with ALCL by design, with 70% of patients enrolled having ALCL. Results from this trial showed that BV-CHP improved both PFS and OS without increasing toxicity compared with CHOP. The 5-year PFS rates in the BV-CHP and CHOP arms were 51.4% and 43%, respectively, and the 5-year OS rates were 70.1% and 61%, respectively.[46] Based on this study, BV-CHP is now recommended in the NCCN guidelines as the standard frontline therapy for ALCL and other CD30-positive T-cell lymphomas.[22]

Although regulatory approval allows for the use of BV-CHP regardless of CD30 expression, use of BV-CHP in those with ≤10% CD30 expression remains controversial. Moreover, in ECHELON-2, the effect of BV-CHP was largely driven by the 70% of patients with ALCL, which uniformly expresses CD30 and is most sensitive to BV. The study was not powered to compare efficacy among individual histologic subtypes, but the benefit of BV-CHP was unclear in PTCL-NOS and AITL, in which CD30 expression is not uniform. Thus, BV-CHP is the standard of care in ALCL, but CHOP remains a standard treatment option for other subtypes. This has prompted interest in investigating other BV-containing frontline combinations in non-ALCL populations. In a phase 2 study of CD30-expressing PTCL (CD30 expression ≥1%), BV-CHP with the addition of etoposide with maintenance BV (with or without consolidative autologous stem cell transplantation) was tolerable and effective, with overall response rates (ORRs) of ~90% regardless of subtype or CD30 expression.[47]

CHOEP is a variation of CHOP with the addition of etoposide. A study of ALK-positive ALCL, AITL, and PTCL-NOS found an OS rate of 61% after 3 years with this regimen. The benefits of etoposide appear to be in the treatment of ALK-positive ALCL, but not in ALK-negative AITL or PTCL-NOS.[48] In a comparison with CHOP, more adverse events (AEs) were noted in the CHOEP group, especially anemia and thrombocytopenia.

Epigenetic Modifying Agents

Romidepsin is an HDACI that selectively inhibits class I HDACs and was granted accelerated approval by the FDA in 2011 primarily based on a single-arm, international, phase 2 study in patients with relapsed or refractory PTCL.[49] A phase 3 study of CHOP ± romidepsin for frontline treatment of PTCL was meant to serve as a confirmatory study for romidepsin approval. However, it failed to meet its primary end point, leading to voluntary withdrawal of romidepsin for the indication of relapsed or refractory PTCL.[50] Nonetheless, the NCCN guidelines continue to list romidepsin as a potential treatment option for initial palliative-intent therapy and for relapsed or refractory disease.[22] Romidepsin is administered on a weekly schedule at a dose of 14 mg/m^2 for 3 of 4 weeks and is associated with nausea, dysgeusia, and, in some cases, prolongation of the QTc interval.

Belinostat, a pan-HDACI with efficacy similar to romidepsin, received accelerated approval in 2014 based on an international, phase 2, single-arm study in 129 patients with relapsed or refractory PTCL. This study demonstrated an ORR of 25.8%, a complete response (CR) rate of 10.8%, and median duration of response (DOR) of 13.6 months.[51] Belinostat is administered daily for 5 consecutive days on a 3-week schedule. AEs include nausea and thrombocytopenia. The confirmatory study for belinostat is an ongoing 3-arm, phase 3 study comparing belinostat-CHOP, pralatrexate-CHOP, and CHOP alone for patients with untreated PTCL (CRESCENDO/NCT06072131).

Azacytidine is a hypomethylating agent that was examined in the phase 3 Oracle study, which compared azacitidine with the investigator's choice of bendamustine, gemcitabine, or romidepsin in patients with relapsed or refractory TFH lymphomas. The study failed to meet its primary end point, which required improvement in PFS with significance of $P<0.025$.[52] With the modest activity of azacitidine observed in this trial, azacytidine may be more appropriate in combination with other agents.

ALK Inhibitors for ALK-Positive ALCL

ALK-positive ALCL is characterized by the activation of the ALK receptor tyrosine kinase by the t(2;5) chromosomal translocation. **Crizotinib** is a small-molecular inhibitor of several tyrosine kinases, including ALK. It demonstrated an ORR of 90% in pediatric patients with relapsed or refractory ALK-positive ALCL.[53] Crizotinib was also evaluated in combination with a standard frontline pediatric regimen for patients with untreated ALK-positive ALCL and demonstrated promising efficacy (2-year event-free survival of 76.8%) but a concerning rate of thromboembolic events (20% before anticoagulation medications were mandated).[54]

In an open-label phase 2 trial of 10 patients (aged ≥6 years; median age, 19.5 years), treatment with **alectinib** (300 mg twice daily except in patients weighing <35 kg, who were given a reduced dose of 150 mg twice daily), resulted in an ORR of 80% with estimated 1-year PFS and OS rates of 58% and 70%, respectively.[55] Alectinib was approved in Japan for relapsed or refractory ALK-positive ALCL based on this study.

Brigatinib has shown efficacy in patients with relapsed or refractory ALK-positive ALCL after prior therapy with BV and crizotinib.[56] In a study of 15 patients with previously treated ALK-positive ALCL brigatinib was associated with an ORR of 93% (73% CR). After a median follow-up of 15 months, the 1-year PFS and OS rates were 72% and 85%, respectively.

PI3-Kinase Inhibition

Duvelisib is a PI3K-δ,γ inhibitor that was investigated in the multicenter phase 2 PRIMO study in patients with relapsed or refractory PTCL. This study demonstrated an ORR of 49% and a CR rate of 34%, with a median PFS of 3.6 months.[57] Although the study was not powered for subgroup analyses, duvelisib appeared to demonstrate preferential activity in certain subgroups (ORR of 67% in AITL and 48% in PTCL-NOS vs 13% in ALCL). Patients with AITL and PTCL-NOS also had significantly longer median PFS of 9.1 months and 3.5 months, respectively, compared with 1.5 months for ALCL.[57] Based on these data, treatment with duvelisib can now be considered, especially for TFH lymphomas, but it carriers risks for transaminitis, colitis, rash, and infection. The potential for frontline use of duvelisib is being evaluated in the ongoing randomized phase 2 Alliance study, in which duvelisib + CHOP is being compared with CHOEP (NCT04803201). Duvelisib combinations with chidamide (NCT05976997) and ruxolitinib (NCT05010005) are also ongoing.

Linperlisib, a PI3K-γ selective agent, has been studied in China, demonstrating a 48% ORR in relapsed or refractory PTCL with a relatively lower rate of diarrhea (14%) and transaminitis (20%–23%), and studies are ongoing in other countries.[58] Given the relatively high ORR and CR rates, PI3K inhibitors are promising in PTCL, where the effectiveness of other therapies is limited.

Hematopoietic Stem Cell Transplantation Consolidation

Hematopoietic stem cell transplantation (HSCT) has been used in consolidation of remissions after frontline therapy and should be considered for patients who are candidates for transplant (**Figure 3**).[59] For those who are not candidates or who have primary refractory disease, survival rates are low.[60,61] These patients

may benefit from allogeneic transplantation if they respond to salvage therapies.

Treatment for Relapsed and Refractory Disease

The selection of second-line (2L) therapy (single agent vs combination regimen) should be based on the patient's age and performance status, donor availability, agents' AE profiles, and the goals of treatment. For instance, if the intent is to transplant, ORR or CR rates may be more important than the ability to give a medication in an ongoing or maintenance fashion without cumulative toxicity. For patients in whom autologous HSCT is imminent, combination chemotherapy before transplantation is often preferred.

Allogeneic HSCT is also a standard of care in eligible individuals with relapsed or refractory disease.[22] OS in relapsed or refractory PTCL *without* allogeneic HSCT is <1 year.[62,63] Combination chemotherapy may be preferred for patients who are ready to proceed to allogeneic HSCT when a suitable donor has already been identified. However, if no donor is available, the use of intensive combination chemotherapy is not recommended due to the inability to maintain a response for longer periods with continuous treatment. For those who do not plan to pursue transplantation or treatment, palliative radiotherapy and/or best supportive care are recommended and should be suggested.[22]

The median PFS in relapsed or refractory PTCL with existing therapies is short (3-4 months).[64] This underscores the need for novel approaches for patients with recurrence. 2L treatment for T-cell lymphomas often involves enrollment in clinical trials, as it provides access to cutting-edge pharmaceuticals. However, trials are not always a good fit for every patient, due to exclusion criteria and other factors.

BV

The safety and efficacy of BV in patients with relapsed or refractory systemic ALCL was initially established in a multicenter phase 2 study.[65] Long-term follow-up results

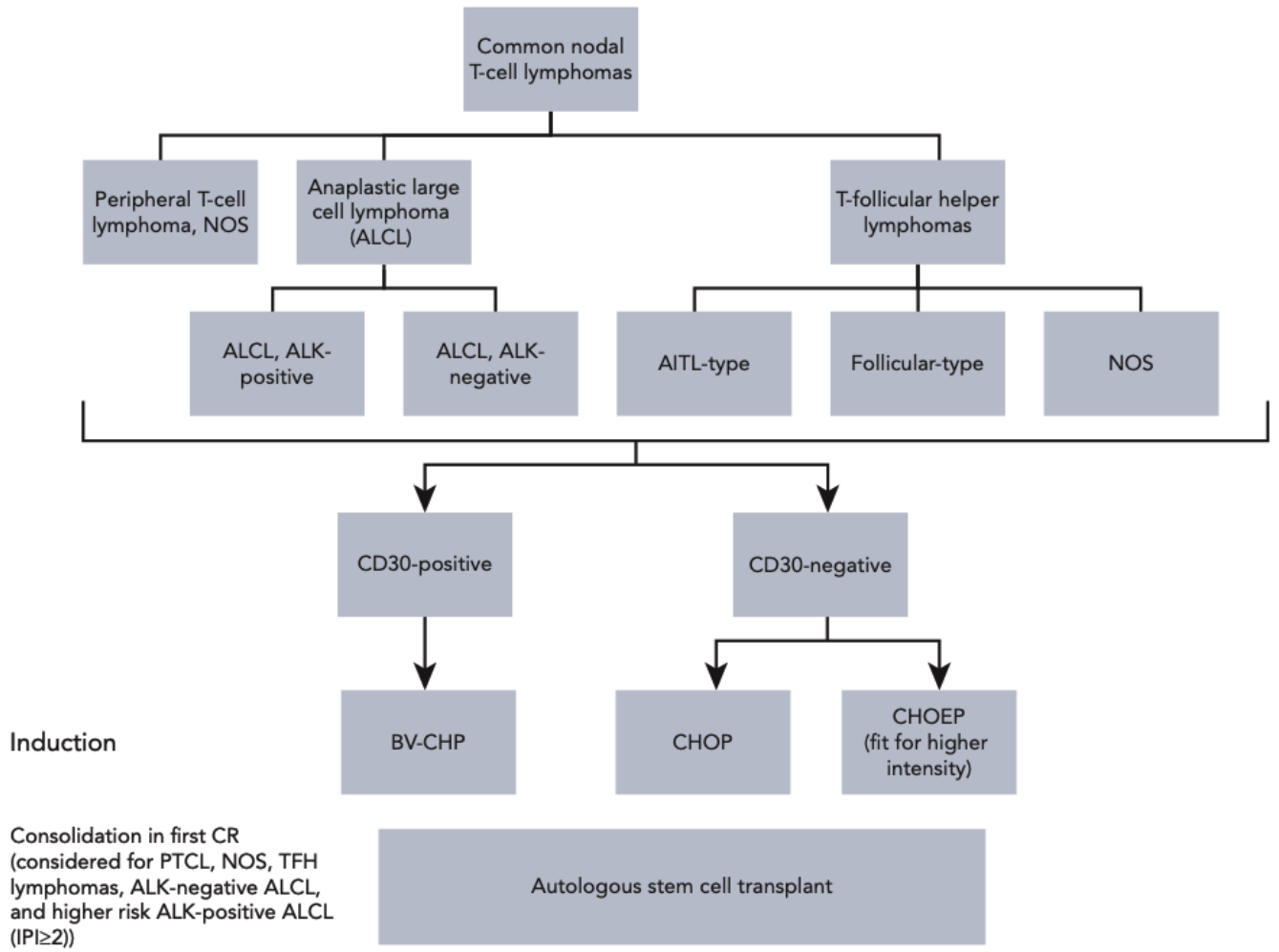

Figure 3. Current frontline treatment for common PTCLs.[59]

AITL, angioimmunoblastic T-cell lymphoma; **ALCL,** anaplastic large cell lymphoma; **ALK,** anaplastic lymphoma kinase; **BV-CHP,** brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisolone; **CHOEP,** cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone; **CHOP,** cyclophosphamide, doxorubicin, vincristine and prednisolone; **CR,** complete response; **IPI,** International Prognostic Index; **NOS,** not otherwise specified; **PTCL,** peripheral T-cell lymphoma; **TFH,** T-follicular helper

Table 3. Combinations of novel agents in patients with PTCL.[77-80]

Agents	Phase	Trial #	Patient population	# evaluable PTCL patients	Efficacy
Romidepsin + pralatrexate[77]	1	NCT01947140	R/R PTCL	14	ORR: 71% mDOR: 4.29 mo mPFS: 4.4 mo mOS: 12.4 mo
Romidepsin + duvelisib[78]	1b/2	NCT02783625	R/R PTCL	48	ORR: 56% CR: 44% mDOR: 12 mo mOS: 12 mo
Romidepsin + azacitidine[79]	2	NCT01998035	Treatment-naïve or R/R PTCL	23	ORR: 61% CR: 48% mDOR: 20.3 mo mPFS: 8 mo mOS: NR
Romidepsin + lenalidomide[80]	1b/2	NCT01755975	R/R PTCL	15	ORR: 53% CR: 13%

CR, complete response; **mDOR,** median duration of response; **mOS,** median overall survival; **mPFS,** medial progression-free survival; **ORR,** overall response rate; **PTCL,** peripheral T-cell lymphoma; **R/R,** relapsed or refractory.

confirmed the durability of clinical benefit with BV in relapsed or refractory systemic ALCL.[66] After a median follow-up of approximately 5 years, the ORR of 86% (66% CR and 21% PR) was similar to the previously reported ORR of 86% (57% CR) as evaluated by an independent review committee. The estimated 5-year OS and PFS rates were 60% and 39%, respectively. The 5-year OS rate was higher for patients who achieved a CR (79% vs 25% for those who did not achieve a CR). The median DOR for all patients was 26 months. The ORRs were similar for patients with ALK-negative ALCL (88%; 52% CR) and ALK-positive ALCL (81%; 69% CR). The estimated 5-year OS and PFS rates were 61% and 39%, respectively, for patients with ALK-negative ALCL. The corresponding survival rates were 56% and 37%, respectively, for those with ALK-positive ALCL. Among patients who achieved a CR, the 5-year PFS rate was 60% for those with ALK-negative ALCL and 50% for those with ALK-positive ALCL. Peripheral neuropathy was the most common AE, reported in 57% of patients, with resolution or improvement reported in the majority with long-term follow-up. In August 2011, based on the results from this study, BV was approved by the FDA for the treatment of patients with systemic ALCL after failure of at least one previous multiagent chemotherapy regimen.[41]

The planned subset analysis of a phase 2 multicenter study that evaluated the efficacy and safety of BV in relapsed or refractory CD30-positive NHL showed that this agent was also effective in other subtypes of relapsed PTCL, particularly AITL.[67] This analysis included 35 patients with PTCL (22 with PTCL-NOS and 13 with AITL); the ORR, median DOR, and median PFS for all patients with T-cell lymphoma were 41%, 7.6 months, and 2.6 months, respectively. The ORR (54% vs 33%) and the median PFS (6.7 vs 1.6 months) were better for patients with AITL than those with PTCL-NOS.

A retrospective study from the LYSA Research Network confirmed the efficacy of BV in combination with bendamustine in patients with relapsed or refractory PTCL (n=82), particularly as a bridge to allogeneic HCT. The ORR was 68%, with a 49% CR rate.[68] After a median follow-up of 22 months, the median PFS and OS were 8.3 months and 26.3 months, respectively. The outcomes were better for patients who underwent allogeneic HCT after achieving CR. In this group, the median PFS was 19.3 months, and the median OS was not reached.

In addition to BV, other CD30-directed therapies, including chimeric antigen receptor T-cell–based therapy and bispecific antibodies, are currently under investigation.

Chemotherapy

In patients with good performance status, 2L chemotherapy may be an option,[62] and a variety of regimens are recommended in the NCCN guidelines. Selected combinations include[22]:

- DHAP, consisting of dexamethasone, cytarabine, and platinum;
- ESHAP, consisting of platinum (cisplatin or oxaliplatin) in addition to etoposide, methylprednisolone, and cytarabine;
- ICE, which also leverages ifosfamide and carboplatin to target disease; and
- Gemcitabine-based approaches, including GemOx (gemcitabine and oxaliplatin), GDP (gemcitabine, dexamethasone, and cisplatin), GVD (gemcitabine, vinorelbine, and liposomal doxorubicin)

Single-agent chemotherapy has also been shown to be effective and may serve as a bridge to allogeneic transplantation. Active single agents listed in the NCCN guidelines include romidepsin, BV, belinostat, duvelisib, and pralatrexate.[22,69] **Pralatrexate**, an antifolate analogue, carries an ORR of 29% with a median PFS and OS of 3.5 and 14.5 months, respectively. The original study used dosing at 30 mg/m^2 weekly for 6 weeks of a 7-week cycle, although with high rates of rash, cytopenias, and mucositis.[69] Toxicities can be mitigated by dosing for 3 weeks of a 4-week cycle and utilizing leucovorin.

Novel Approaches

Novel targeted therapies in development for relapsed or refractory T-cell lymphomas are demonstrating efficacy in clinical trials. One new area involves the inhibition of este homolog 1 and 2 enhancers (EZH1/2s). **Valemetostat**, a medication with this mechanism of action, was recently approved in Japan.[70] In the pivotal phase 2 VALENTINE-PTCL01 trial, conducted in patients with relapsed or refractory adult T-cell leukemia/lymphoma, the ORR was 43.7%, the CR rate was 14.3%, OS was 17 months, and PFS was 5.5 months.[71] Another dual EZH1/2 inhibitor, **HH2853**, is in early-stage development. It demonstrated an ORR of 60.7% and a CR rate of 21.4% in relapsed or refractory PTCL in a phase 1b study.[72] A phase 3 confirmatory study of valemetostat in PTCL is in development. Given the efficacy and safety profile, EZH2 inhibitors are promising both as single-agents and in combination but are not currently approved for standard use outside of Japan.

Preclinical data show that activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway may mediate the pathogenesis of PTCL, making it a

promising target. **Ruxolitinib,** a JAK1/2 inhibitor, was investigated in a phase 2 study involving patients with both relapsed or refractory PTCL and CTCL. Biomarker-driven cohorts were established based on the presence of activating mutations in the JAK/STAT pathway or overexpression of pSTAT3 by IHC. Among 45 patients with PTCL, ORRs were 37% and 36% in those with JAK/STAT-activating mutations or pSTAT3 overexpression, respectively, compared with only 7% in patients without JAK/STAT activation.[73]

Golidocitinib is a selective JAK1 tyrosine-kinase inhibitor. In JACKPOT8 Part B, a single-arm, multinational, phase 2 study exploring the safety and efficacy of golidocitinib in relapsed or refractory PTCLs, the ORR was 44% and the CR rate was 24% after a median follow-up period of 13 months. Grade 3/4 treatment-related AEs occurred in 59% of participants.[74] Given its tolerability and efficacy, golidocitinib is an encouraging, well-tolerated agent with a potential use in PTCL.

Chidamide is an oral selective class I HDACI that was approved in China in 2014 based on a single-arm phase 2 study of 79 patients with relapsed or refractory PTCL. This trial demonstrated an ORR of 28% and a CR rate of 14% in intent-to-treat patients, with an ORR of 50% in patients with AITL.[75] Currently, chidamide is only available in China, and several studies examining chidamide-based regimens are ongoing.

Interleukin-2-inducible kinase (ITK) is an important mediator for T-cell receptor signaling. Studies have shown upregulation or aberrant activation of ITK in AITL and other nodal TFH lymphomas. One ITK inhibitor, **soquelitinib,** demonstrated tumor responses in heavily pretreated PTCLs in a phase 1/1b clinical trial, with a phase 3 study in development.[76]

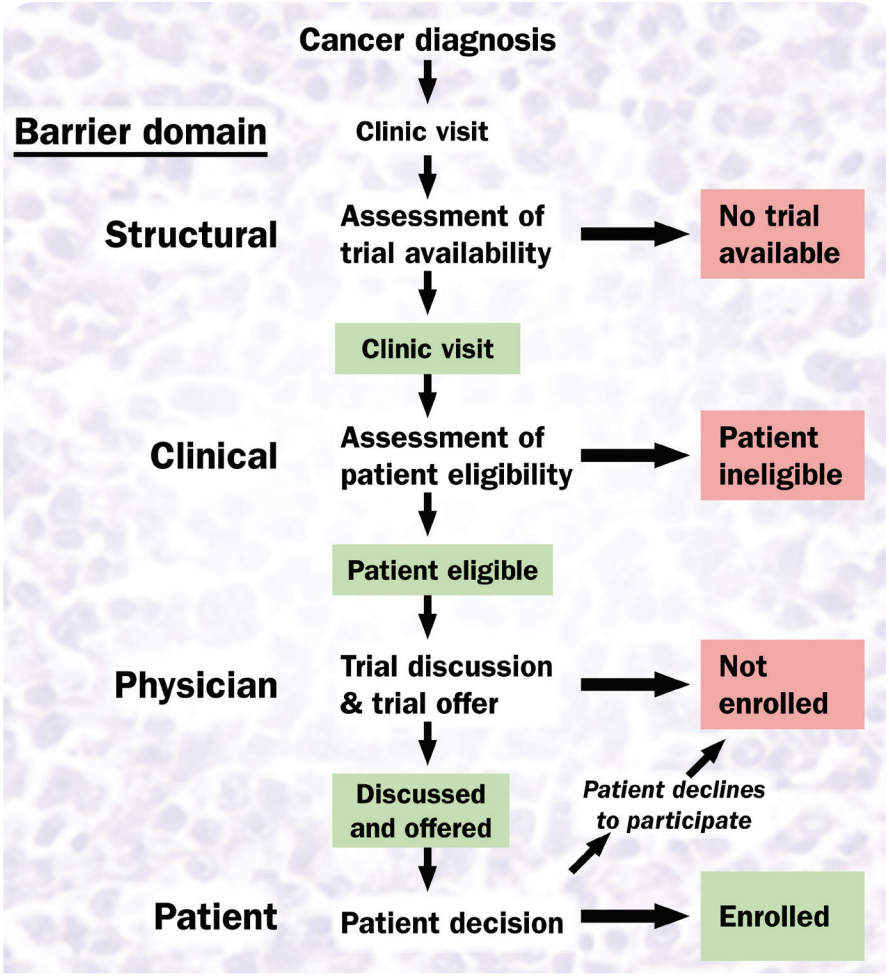

Figure 4. Cancer clinical trial decision making framework.[84]

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Combinations of Novel Agents

Whereas novel agents have primarily been studied as monotherapy, numerous studies have evaluated combinations of novel agents or the addition of novel agents to chemotherapy. Several romidepsin-based combinations have demonstrated efficacy in patients with PTCL (**Table 3**),[77-80] and thus, combinations of novel agents may represent important treatment options in the future.

Shared Decision Making in Oncology

Patients and providers are encouraged to engage in shared decision making (SDM) to determine optimal therapeutic approaches that can be based on a variety of complex, intermingling factors. Patients have different support needs; physicians who take a personalized approach to SDM can streamline the process and improve the patient experience. Patient-readiness aids are especially helpful for identifying individual needs.[81]

Once patient readiness is established, value clarification is critical to SDM, particularly where early-phase clinical trials are concerned. It is important to understand patients' perspectives on a wide variety of principles and values. This ensures the incorporation of personal values in SDM, thus improving both the process itself and patient outcomes.[82] Design-based, data-driven decision-support tools can also be used to encourage personalized care and empower patients to feel more in control of their treatment journey. These tools are underutilized in clinical practice.[83]

Clinical Trials in Oncology

Patient participation in clinical trials forms the backbone of cancer clinical research. Clinical trials are the key step in advancing new treatments and improving outcomes. With greater participation, trials can be conducted more rapidly and efficiently, and novel therapies can be discovered more quickly, benefitting all patients with cancer. Additionally, trials offer patients the opportunity to access the newest available treatments, so access to trials should be equitable and easy for interested individuals.[84]

Unfortunately, most adult patients with cancer do not participate in clinical trials. In fact, it is believed that enrollment rates in this population are only 2% to 3%,[85] despite the fact that most Americans have a favorable view of

Case Study

Presentation and Diagnosis

Joyce is a 60-year-old elementary school teacher. She presents with fatigue, night sweats, rash, and peripheral adenopathy. Laboratory assessment shows anemia (hemoglobin 9.8 g/dL) and elevated serum lactate dehydrogenase (360 U/L). FDG-PET/CT shows 2- to 3-cm axillary, mediastinal, inguinal, and retroperitoneal lymphadenopathy. Excisional biopsy of an axillary lymph node reveals atypical lymphocytes expressing CD3, CD5, CD10, BCL6, PD-1, and ICOS. Bone marrow biopsy shows 10% involvement with lymphoma. She is diagnosed with nodal TFH lymphoma, angioimmunoblastic subtype.

Treatment and Recurrence

Joyce completes 6 cycles of CHOEP and has a complete metabolic response on imaging. Fourteen months later, she presents with new axillary lymphadenopathy. FDG-PET/CT reveals FDG-avid bilateral axillary and retroperitoneal lymphadenopathy. Core needle biopsy of a left axillary lymph node confirms recurrent nodal TFH lymphoma, angioimmunoblastic subtype with 10% CD30 expression.

Subsequent Treatment

Joyce is started on treatment with BV and initially has a partial remission by PET/CT. Four months later, PET/CT reveals new FDG-avid bulky lymphadenopathy within the retroperitoneum. Joyce is eager to discuss further options for treatment, including clinical trials.

clinical trial involvement.[86] The gap between the willingness of patients to participate in trials and their actual participation rates suggests the presence of numerous barriers, many of which are modifiable (**Figure 4**).[84]

Conclusion

Non-Hodgkin T-cell lymphomas are a heterogeneous group of blood cancers that are associated with poor outcomes and frequent relapse. Clinicians can streamline diagnosis and treatment via thorough analysis of biomarkers and accurate subtyping by IHC. Consensus on optimal frontline approaches is lacking, but recent data show that the incorporation of BV with CHOP has improved PFS and OS in CD30-expressing T-cell lymphomas. Consolidation with autologous transplantation remains a standard for transplant-eligible patients in first remission, but there remains no consensus on the management of relapsed and refractory disease. Novel agents and targeting strategies are in development to address the underlying biology of the different subtypes of T-cell lymphoma and hopefully will be implemented in future treatment algorithms. Finally, the approach to aggressive T-cell lymphoma requires multispecialty collaboration for diagnosis and management of this complex group of diseases.

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