Diagnosis and treatment of peripheral T-cell lymphomas: Update recommendations of the Belgian Hematology Society (BHS)

Treatment of extra-nodal and leukemic T-cell lymphomas will be discussed in another dedicated BHS guideline

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SUMMARY

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of aggressive diseases associated with poor outcomes. Recent progress in understanding of the biology and pathogenesis based on molecular profiling and next-generation sequencing has led to the introduction of new provisional entities in the World Health Organization (WHO) classification system of 2017 and to the emergence of new drugs.[1] Previous Belgian guidelines were published in 2013.[2] This review will discuss the diagnosis, work-up and treatment of PTCL including these advances as well as the limitation of the availability of drugs according to the Belgian reimbursement rules.

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CLASSIFICATION

PTCL derive from mature post-thymic cells and commonly arise in nodal tissue as well as in extranodal sites. They represent 10-15% of non-Hodgkin lymphomas in Western countries.[3] In Asia, up to 20% of lymphoma patients suffer from NK/T-cell lymphomas.[3]

The WHO classification of hematopoietic and lymphoid tumours divides PTCLs into nodal, extranodal and leukemic types, each with multiples entities. The 2017 update incorporated advances in understanding of the cell of origin and the molecular signatures of different types of PTCL.[1]

Peripheral T-cell lymphoma not otherwise specified (PTCL, NOS) refers to subtypes of PTCL that are not classifiable into distinct entities and is the most common category, accounting for 30-35% of PTCL cases. PTCL, NOS are considered to be nodal lymphomas although extranodal

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TABLE 1. Classification of mature T and NK neoplasms based on the 2017 WHO classification.[1]

Nodal	• PTCL not otherwise specified (PTCL-NOS) • Anaplastic large-cell lymphoma (ALCL), ALK+ or ALK - • Angioimmunoblastic T-cell lymphoma (AITL) • Follicular T-cell lymphoma • Nodal peripheral T-cell lymphoma with TFH phenotype
Extranodal	• Pleiomorphic enteropathy-associated T-cell lymphoma (EATL) • Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL, formerly EATL type 2) • Indolent T-cell lymphoproliferative disorder of the GI tract • Extranodal natural killer/T-cell lymphoma (ENKTCL), nasal type • Hepatosplenic T-cell lymphoma (HSTCL) • Panniculitis-like T-cell lymphoma (αβ subtype) • Breast implant-associated anaplastic large-cell lymphoma
Leukemic	• Adult T-cell leukaemia/lymphoma (ATLL) associated with HTLV-1 • T-cell prolymphocytic leukaemia • Large granular lymphocytic leukaemia • Aggressive NK-cell leukaemia • Chronic lymphoproliferative disorder of NK cells

initial involvement or at relapse is possible. Molecular profiling studies might enable us to distinguish PTCL, NOS from other entities and to identify subtypes. A proportion of the PTCL, NOS might have TFH (T follicular helper) signature, and this might influence future treatment strategies. Then, there is two major molecular subgroups in gene expression profiling studies with different prognosis (GATA3 and TBX21)(*Table 1*).[4]

Anaplastic large-cell lymphoma (ALCL) is characterised by sheets of pleiomorphic cells, typically large anaplastic cells with abundant cytoplasm, vesicular chromatin and variably prominent nucleoli. Different morphologic patterns can be seen in ALK+ ALCL including small cell (5-10%), lymphohistiocytic (10%) and Hodgkin like pattern (<5%).

Angioimmunoblastic T-cell lymphoma (AITL) was at first considered like a dysregulated immune response, but clonality studies have established its malignant issue. Gene expression studies suggest that TFH cells is the cell of origin in AITL.[5] Normal TFH cells provide essential support for B-cell immune response, explaining why many of the clinicopathological feature or AITL reflect immune activation. Lymph node biopsies show a heavy stromal infiltrate comprising plasma cells, eosinophils, histiocytes, and immunoblasts. Malignant T cells may represent a minor component of the infiltrate making the diagnosis challenging. This entity often presents with large scattered CD20 positive, EBER positive immunoblasts.

Two new provisional entities with TFH features (WHO 2017):[1]

- TFH-like PTCL or nodal follicular T cell-related lymphomas (TFH) have been described in recent studies. There is a lack of typical morphological AITL features, but expressing TFH markers (at least two to three). Molecular TFH signature is found in approximately 20% of PTCL-NOS cases, suggesting an overlap with AITL.
- Follicular PTCL is a rare subtype with a follicular infiltrate of malignant T cells derived from TFH cells, with a similar gene expression profile.[6,7]

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is recently recognized by the WHO as a separate entity. The disease most often presents with a delayed seroma around the breast implant, almost exclusively with a textured surface, and manifests with breast pain, swelling or asymmetry, capsular contracture, but can also present with a breast mass, and lymph node involvement. The prognosis of BIA-ALCL is favourable compared with many other subtypes of systemic T-cell lymphoma. It should be noted that there is a Belgian registry ongoing for BIA-ALCL. It is mandatory to declare these cases at the FAGG/AFMPS.

Intestinal PTCL are highly aggressive lymphomas involving intraepithelial T cells, and can be divided in two forms:

- Pleiomorphic enteropathy-associated T-cell lymphoma (EATL) that occurs in the presence of gluten enteropathy,

TABLE 2. Characteristics of key types PTCL subtypes.[1,9-13]

Type of T-cell lymphoma	Immunophenotypic features CD	Others	TCR	Cell of origin	Genetic features
Nodal					
PTCL-NOS	CD4>CD8 CD5 ↓/- CD7 ↓/- CD30 +/- CD56 -/+	Subset with TFH features, cytotoxic granules -/+	αβ, rarely γδ	Mostly T helper cell	Two entities with different prognosis : GATA-3 and its target genes (CCR4, IL18RA, CXCR7, IK) with key role in regulating T helper cell 2 differentiation. Associated with worse outcomes. TBX21 and EOMES and their target genes (CXCR3, IL2RB, CCL3, and IFNg) which regulate T helper cell 1 differentiation.
AITL	CD4 + CD10 +/-	BCL6 +/- CXCL13+, PD1+ ICOS+ SAP +/- CCR +/- hyperplasia of follicular dendritic cell, EBV+ B blasts	αβ	TFH	TET2, DNMT3A and IDH2 epigenetics modifiers mutations are common. RHOA G17V also reported in 50-70% (exact function not elucidated) Mutations in genes involved in TCR signalling (CD28, PCLG1, FYN) also described
ALCL ALK +/-	CD4 -/+ CD8 +/- CD3 -/+ CD2 + CD25+ CD30+ (100%)	EMA+, cytotoxic granules+	αβ	cytotoxic T lymphocyte	t(2;5) in ALK+ BCL6, PTPN12, CEBP, SERPINA1 are preferentially overexpressed in ALK+ ALCL CCR7, CNTFR and IL22 are preferentially overexpressed in ALK- ALCL Rearrangements of DUSP22 and TP63 genes recently founded in 30% and 8% of ALK- ALCL
Extranodal					
EATL	CD8 (+)/- CD56-	HLA-DQ2/8	αβ	Intra-epithelial T cells, pre-existing enteropathy	Mutations in JAK-STAT are frequent
MEITL	CD8+ CD56+		γδ or αβ	Intra-epithelial T cells or NK, no pre-existing enteropathy	Mutations in SETD2, KRAS and STAT5B Mutations in JAK-STAT are frequent
ENKTCL	CD3 +/-, CD56+ CD8 +/-	Granzyme B+ TIA-1+ perforin + EBER+ LMP1	Germline configuration, rarely xb or gd	NK, less commonly Cytotoxic T lymphocyte	Expression of EBV-encoded transcripts and oncogenetic proteins (LMP1, LMP2)
HSTCL	CD4-, CD8+/, CD3+, CD5-, CD56+/-	TIA-1+ Granzyme M+ Granzyme B- Perforin-	γδ, rarely αβ	Cytotoxic T lymphocyte	Trisomy 8 and isochromosome 7q Mutations of SETD2, INO80, ARID 1B, STAT3, STAT5B, PIK3CD have seen

***AITL: angioimmunoblastic T-cell lymphoma, ALCL: anaplastic large-cell lymphoma, ATLL: adult T-cell leukaemia/lymphoma, EATL: enteropathy-associated T-cell lymphoma, ENKTCL: extranodal natural killer/T-cell lymphoma, HSTCL: hepatosplenic T-cell lymphoma, MEITL: monomorphic epitheliotropic intestinal T-cell lymphoma, PTCL-NOS: peripheral T-cell lymphoma not otherwise specified, TFH-related: follicular helper T cell-related.*

and typically on a background of treatment-refractory celiac disease. It occurs occasionally de novo.

- Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), formerly EATL, is not associated with enteropathy or celiac disease and displays a distinct immunophenotype from EATL.

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract is an extremely rare T-lymphoma with very low proliferation fraction, typically less than 10%. Misdiagnosed is significant.

Hepatosplenic T-cell lymphoma (HSTCL) is a rare variant of extranodal PTCL that may be associated with inflammatory bowel disease treated with multiple immunosuppressors. Histological typical features are a significant sinusoidal infiltration in the liver, spleen and bone marrow with medium size cytotoxic T cells. This entity is associated with dismal prognosis.

Extranodal NK/T cell lymphoma, nasal type (ENKL), is a rare lymphoid neoplasm more frequent in Asia, Central and South America, than in occidental countries, characterised by an association with Epstein-Barr virus (EBV). Some studies also showed an overexpression of Programmed death-ligand 1 (PD-L1) on the tumoural cells, suggesting its role in escaping the immune response induced by EBV antigens and a therapeutic target for immune checkpoint blockade.[8] The most frequent structural variations involving programmed death ligands in Epstein-Barr virus-associated lymphomas. The most frequent occurrence sites include the nasal cavity and adjacent sites.

Adult T-cell leukaemia/lymphoma (ATLL) is a distinct subtype of PTCL due to human T-cell lymphotropic virus 1 (HTLV1). It is common in areas were HTLV-1 is endemic like south-west Japan, west Africa, Caribbean, and Brazil. There are four clinical subtypes (acute, lymphoma, chronic and smoldering), based on the presence/absence of leukemic changes, high LDH levels, hypercalcemia and organ infiltration. These subtypes have different treatments strategies.

EPIDEMIOLOGY

Frequency of subtypes of PTCL varies with ethnic and geographic distribution. Rates of nodal PTCL are generally highest in black ethnic groups, followed by white and Asian groups, with subtypes variations.[14] In Europe, nodal subtypes are more frequent in Caucasian patients with 34% PTCL-NOS, 28% AITL, 6% ALK+-ALCL, 9% ALK-ALCL.[3,11] Then, EATL is more common in areas with a high incidence of celiac disease, EBV-associated lymphoproliferative T- and NK-cells neoplasms are more commonly seen in East Asian countries such as Korea and northern China. The distribution of lymphomas associated with human T-cell lymphotropic virus type 1 (HTLV-1) follow the distribution of the virus, in Japan and the Caribbean basin.[3,11]

Overall frequency of the different subtypes of PTCL from the International PTCL project is based on retrospective analysis of 1,314 cases of previously untreated PTCL or ENKTCL diagnosed at 22 centres in the world between 1990 and 2002.[3]

In Belgium, recent data have concluded that peripheral T cell lymphomas are more frequent in the elderly population. Between 2004 and 2008, the incidence rate is increasing in Belgium, mainly in the age group 70 years and older. Regarding survival, the relative survival is higher in females than in males and decreases significantly with age, and depends on the subtype. The results suggest an improvement of the 5-year relative survival over time (from 47% in 2004-2008 to 53% in 2014-2018).[15]

CLINICAL PRESENTATION, DIAGNOSIS AND BASELINE STAGING

The diagnosis and subtyping of PTCL remains a challenge and requires clinical, biological, pathological, flow cytometry, molecular and genetic biology integration. The morphology indicates the neoplastic nature of a given T-cell population; aberrant T-cell phenotype and clonality based on T-cell receptor (TCR) genotype (i.e. alpha/beta versus gamma/delta). Evidence indicates the TCR genotype and the cell of origin influence tumour biology and clinical evolution. It seems to be crucial because it could determine both prognosis and choice of therapy.

Presentation:[16] The symptoms of PTCL are very variable. Although the only sign is often an enlarged painless lymph node, some patients also experienced B symptoms. Skin rash may be present, particularly in patients with PTCL-NOS or AITL. Hypotension, fevers, rash, vasculitis-like symptoms may be present in patients with AITL, due to tumour-related cytokine release. Other symptoms depend on the location. Then, ALCL is frequently associated with cutaneous nodules also in the systemic variants.

Diagnostic work up:[17] Physical examination is crucial, with attention to lymph node groups, liver, and spleen and skin. B symptoms should be evaluated and performance status determined. In the biology, complete blood count, LDH, renal, hepatic and acid uric functions should be monitored. Cardiac evaluation is required prior to chemotherapy.

Excisional or incisional biopsy is preferred over core needle biopsy. Given the heterogeneity of many T-cell lymphomas and to obtain suitable tissue for flow cytometry, multiple

cores should be obtained where possible.

The immunohistochemistry panel and should include general T-cell markers (CD3, CD2, CD5, CD7) and B-cell marker CD20. Depending on the morphological changes, additional immunohistochemical studies to characterize subsets of T-cells may be necessary, including markers of T-follicular helper (TFH) cell of origin (CD4, CD10, BCL6, PD1, ICOS, CXCL13), NK/T cell markers (CD56), and cytotoxic T-cell markers (CD8, cytotoxic markers granzyme B, perforin, TIA1) may be helpful. Other helpful markers are the TNF receptor superfamily member CD30, the proliferation marker Ki67 and CD21/CD23, used to detect follicular dendritic cells in AITL. Expression of ALK is always abnormal, and most often due to a fusion protein related to a translocation. Loss of mature T-cell markers is often found (most frequently CD7, CD5 or CD2). T-cell receptor gene rearrangement is shown via PCR (TCR Beta and Gamma). Epstein-Barr virus (EBV) encoding region (EBER) in situ hybridization should be considered in cases suspected to be nasal ENKTCL and AITL. Molecular analysis should include PCR to detect TCRbeta or TCRgamma gene rearrangements, and FISH to detect genetic alterations (ALK, TP63, and DUSP22).

At diagnosis and relapse, a bone marrow biopsy is still recommended because 30% of PTCL NOS cases show bone marrow involvement. Bone marrow aspirate should be sent for flow cytometry and gene rearrangements studies.

Whole body imaging is required for accurate staging with chest/abdominal/pelvic CT with contrast, or with PET-CT, more useful in extranodal disease. In PTCL, FDG avidity at baseline is heterogeneous and it seems to depend on the type of PTCL, higher in anaplastic large cell lymphoma than in angioimmunoblastic T-cell lymphoma for example.[14]

Assessment of HTLV 1, HIV, HCV and HBV, skin biopsy, head CT or MRI, CSF analysis if clinical suspicion or EBV PCR may be required especially in the setting of AITL and NK/T lymphomas. A colonoscopy is useful for the enteropathy subtypes.

Fertility issues and options of gametes cryopreservation to be discussed.

Baseline staging: Despite most PTCL are aggressive, the Ann Arbor staging system is preferred.

Response assessment: Regarding the predictive value of interim PET-CT in T cell lymphoma, the data are based on retrospective studies and are few conclusive.[16,17] Despite the prognostic utility is controversial, we recommend a mid-treatment PET-CT evaluation (after three cycles). Based on the available data, computed tomography (CT) is also reasonable. The post-treatment imaging study of choice is the PET-CT, which provides information on the size and activity of residual masses and allows for the distinction between active disease and fibrosis. It should be performed six to eight weeks after completion of chemotherapy, and twelve weeks after the completion of radiation therapy.[18]

TABLE 3. Incidence of PTCL subtypes in the International PTCL Project.[3]

Subtype	Frequency (%)
PTCL-NOS	25.9
AITL	18.35
ALCL ALK + ALK -	 6.6 5.5
ENKTCL	10.4
Enteropathy-associated	4.7
HSTCL	1.4

PROGNOSIS FACTORS AND SCORES

The majority of T-cell lymphoma are aggressive diseases associated with inferior prognosis compared to the B-cell lymphoma.[19] For example, the International T-cell Lymphoma study reported overall survival and failure-free survival of 10% at ten to fifteen years in patients with PTCL-NOS.[3]

In general, ALCL has a better prognosis than the other entities, especially if ALK+ (5yr OS: 65-90% *vs.* 30-50%).[20,21]

Several prognostic indices taking laboratory and clinical features into account have been proposed. Some prognostics factors are specific in the different PTCL subtypes.

The classical international prognostic index, or IPI, was developed in 1993 to identify factors that predict the prognosis of patients with aggressive NHL has been shown to predict survival in patients with ALCL, AITL and PTCL-NOS, but not for other PTCL entities.[22] It is probably the most representative with the Age-adjusted international Prognostic Index (*Tables 3 & 4*).[22]

The Prognostic Index for T-cell lymphomas (PIT) based on retrospective univariate analysis of data from 385 PTCL-NOS cases should provide more accurate prognostic information for PTCL subtypes (*Table 5*).[23]

Prognostic Index for PTCL-Unspecified (or modified -PIT) was developed by *P. Went and al* in 2005 and is based on a

TABLE 4. International prognostic index.

RISK FACTORS, all patients	International index	International index	Distribution (%)	5 year OS (%)
Age > 60 years Serum LDH > normal ECOG PS 2-4 Stage III or IV Extranodal involvement > 1 site	Low	Low	35	73
	Low-intermediate	Low-intermediate	27	51
	High-intermediate	High-intermediate	22	43
	High	High	16	26

TABLE 5. Age-adjusted international Prognostic Index, patients ≤ 60 years.

RISK FACTORS, patients ≤ 60 years	International index	Factors	Distribution (%)	5 year OS (%)
Stage III or IV Serum LDH > normal ECOG PS 2-4	Low	0	22	83
	Low-intermediate	1	32	69
	High-intermediate	2	32	46
	High	3	14	32

TABLE 6. Prognostic index for PTCL unspecified (PIT).

RISK FACTORS	Prognostic Risk	Factors	5 year OS (%)	10 year OS (%)
Age > 60 years Serum LDH > normal ECOG performance status 2-4 Bone marrow involvement	Group 1	0	62	55
	Group 2	1	53	39
	Group 3	2	33	18
	Group 4	3 or 4	18	13

TABLE 7. Prognostic Index for PTCL-U (Modified -PIT).

RISK FACTORS	Prognostic risk	Factors	Median survival (range)
Age > 60 years Serum LDH > normal ECOG PS 2-4 ki-67 > or = 80%	Group 1	0 or 1	37 months (1-135)
	Group 2	2	23 months (1-138)
	Group 3	3 or 4	6 months (2-11)

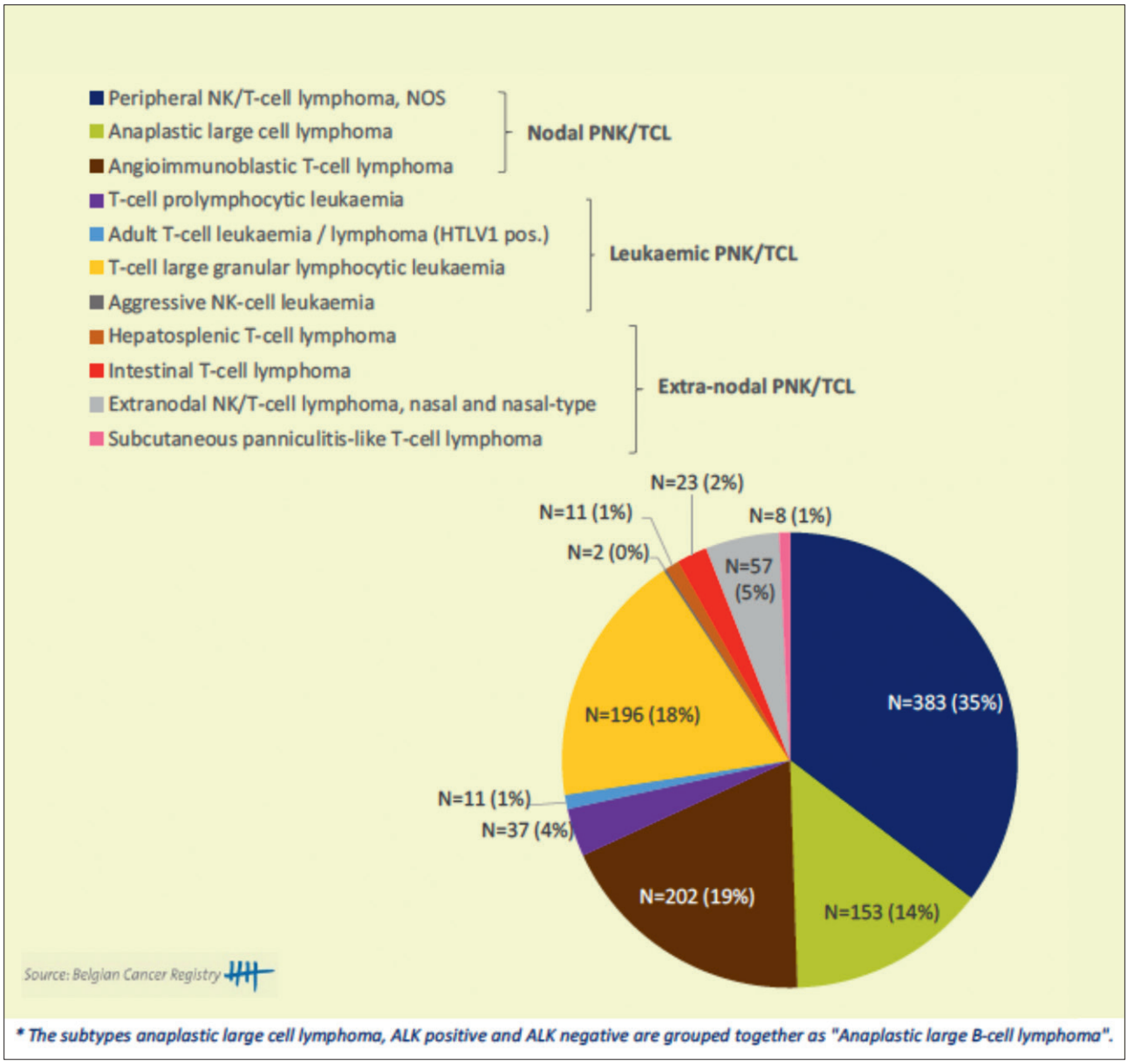

FIGURE 1. Updated incidence by subtype in Belgium, 2013-2018.[15]

retrospective analysis in 93 PTCL patients. This score includes age, high lactate dehydrogenase, poor performance status and Ki67 level (*Table 6*).[24]

Prognostic index of natural killer lymphoma (PINK) and Prognostic index of natural killer cell lymphoma with Epstein-Barr virus DNA (PINK-e) are used for the extranodal NK/T-cell lymphoma (*Table 7*).[25]

ALCL without involvement of the anaplastic lymphoma kinase (ALK neg): DUSP22 rearrangements are associated with decreased expression of dual-specificity phosphatase-22, an enzyme that regulates mitogen-activated protein kinase signalling. Retrospectives and prospective studies found that DUSP22 rearrangements were associated with favourable outcomes in ALK-negative ALCL. Then, TP63 rearrangements encoding p63 fusion proteins were associated with aggressive clinical behaviour and poor outcomes. Triple negative ALCLs would have intermediate OS rates inferior to those of DUSP22-rearranged ALCLs and superior to those of TP-63 rearranged cases.[20,21,26] However, the positive impact of the presence of DUSP22 rearrangement has recently found to be controversial in a recent publication in the *British Journal of Haematology*, who found lower outcomes in eleven patients with DUSP22 rearrangement[27]. Further large-scale studies are needed to fully understand the spectrum of ALK- ALCL.

Chemokine expression, proliferative signature or some biological factors have also been shown to have prognostic significance, but they can be used in daily practice. Biological

TABLE 8. Extranodal NK/T-cell lymphoma: Prognostic index of natural killer lymphoma (PINK).

RISK FACTORS	Factors	PINK	3 year OS
Age > 60 years Stage III-IV Distant lymph-node involvement Non-nasal type disease	0	Low-risk	81%
	1	Intermediate-risk	62%
	2 or more	High-risk	25%

TABLE 9. Prognostic significance of biological factors in PTCL.

Worse	Favourable	Variable
p53 ki-67 BCL-2, BCL-XL CD26 EBV MDR CCND2 CCR4 PRMDM1 TCR g1	NK-kB CCR3 ALK-1 TCR BF1	CXCR3

factors are resumed in the *Table 8*.[10]
Others factors like CD3 expression or anaemia could have a prognostic impact but further studies are needed to confirm.[28]

UP FRONT THERAPY

The main goal of first-line treatment should be to achieve complete remission and long-term control of the disease, if not a cure. Anthracycline-based regimens are considered the current standard of care in induction treatment of PTCL patients. A meta- analysis by *Abouyabis et al*. showed that anthracycline-based regimens used as an induction strategy could induce a CR rate for PTCL patients ranged from 35.9% for enteropathy-type T-cell lymphoma (ETTL) to 65.8% for anaplastic large cell lymphoma (ALCL). But with a high rate of disease relapse or progression, yielding a 5-year OS of 38.5% for all PTCL patients.[29]
In these guidelines, we will focus only on the most common nodal PTCL, because extra-nodal entities such as ENKTCL or EATL/MEITL or BI-ALCL and leukemic forms have different treatments options. Management of these rare features will be the subject of a next publication.

HOW TO DO BETTER THAN CHOP?

INTENSIFICATION

More intensive chemotherapy regimens have not proven to be more effective than CHOP in historical controls; moreover, the only phase III randomised study comparing an alternative induction schedule including etoposide, ifosfamide, and cisplatin, alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine with CHOP (given every 21 days) did not show any superiority in terms of event-free survival (EFS) and overall survival (OS), thus confirming CHOP as the reference regimen for PTCL patients.[30]

CHOP + X

ETOPOSIDE

The role of adding etoposide to CHOP (CHOEP) was investigated by the German High-Grade Non-Hodgkin Lymphoma Study Group: CHOEP, given either every 14 or 21 days, significantly improved response and 3-year EFS rates (70.5% after CHOEP *vs.* 51.0% after CHOP) in young patients (18-60 years) with normal LDH levels, although 3-year OS did not significantly differ between the two groups (81.3% for CHOEP *vs.* 75.2% for CHOP). Therefore CHOEP failed to enhance clinical outcomes in patients older than 60 years, for whom CHOP should remain the standard first-line approach.[31] Similarly, an analysis of real-world data from the Swedish Lymphoma Registry showed a progression free survival benefit for CHOEP in patients aged 60 year and younger, but without an improvement in overall survival.[32] More recently, a large analysis of adult patients with ALK-positive ALCL (n=263) supports that integration of etoposide into the primary therapy may be associated with important improvements in PFS 5y (83% *vs.* 62%) and OS 5y (93% *vs.* 74%).[33]

BRENTUXIMAB VEDOTIN

Expression of CD30 is uniformly strong in systemic anaplastic large cell lymphomas, which comprise approximately 12% of all peripheral T-cell lymphomas, whereas

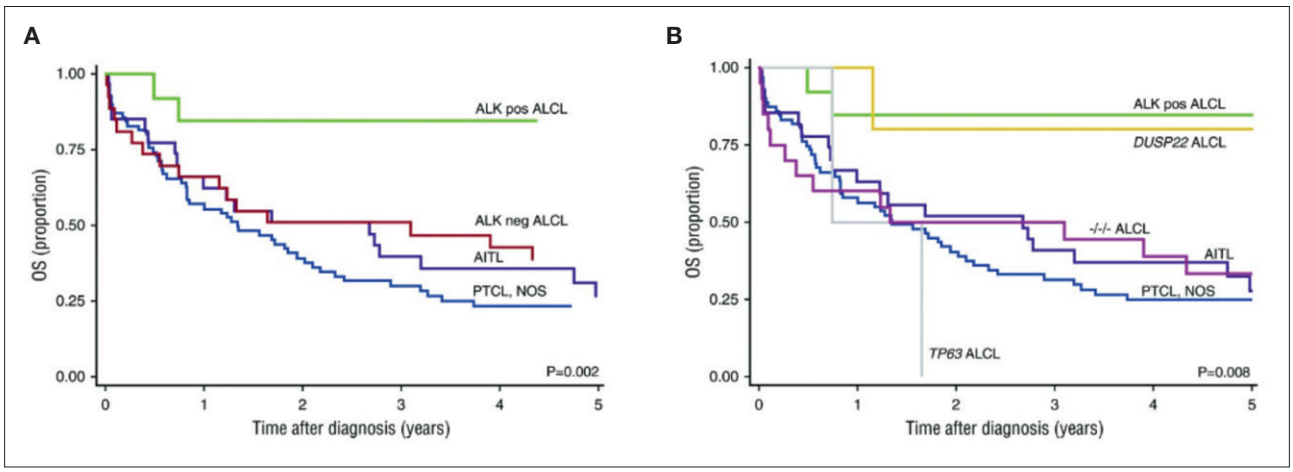

FIGURE 2. Different prognosis according to subgroups.[20,21]

in other peripheral T-cell lymphoma subtypes, CD30 expression is more variable with overall rates of CD30-positivity ranging from 43% to 57%, according to the cut-offs used. Brentuximab vedotin is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule disrupting drug monomethyl auristatin E.

Very recently, *S. Horwitz et al.* present the results of a pivotal phase III, randomised, double-blind, multicentre trial (ECHELON-2) directly comparing the regimens of CHOP versus BV CHP in treatment-naive patients with CD30-positive (defined as ≥10% cells) peripheral T-cell

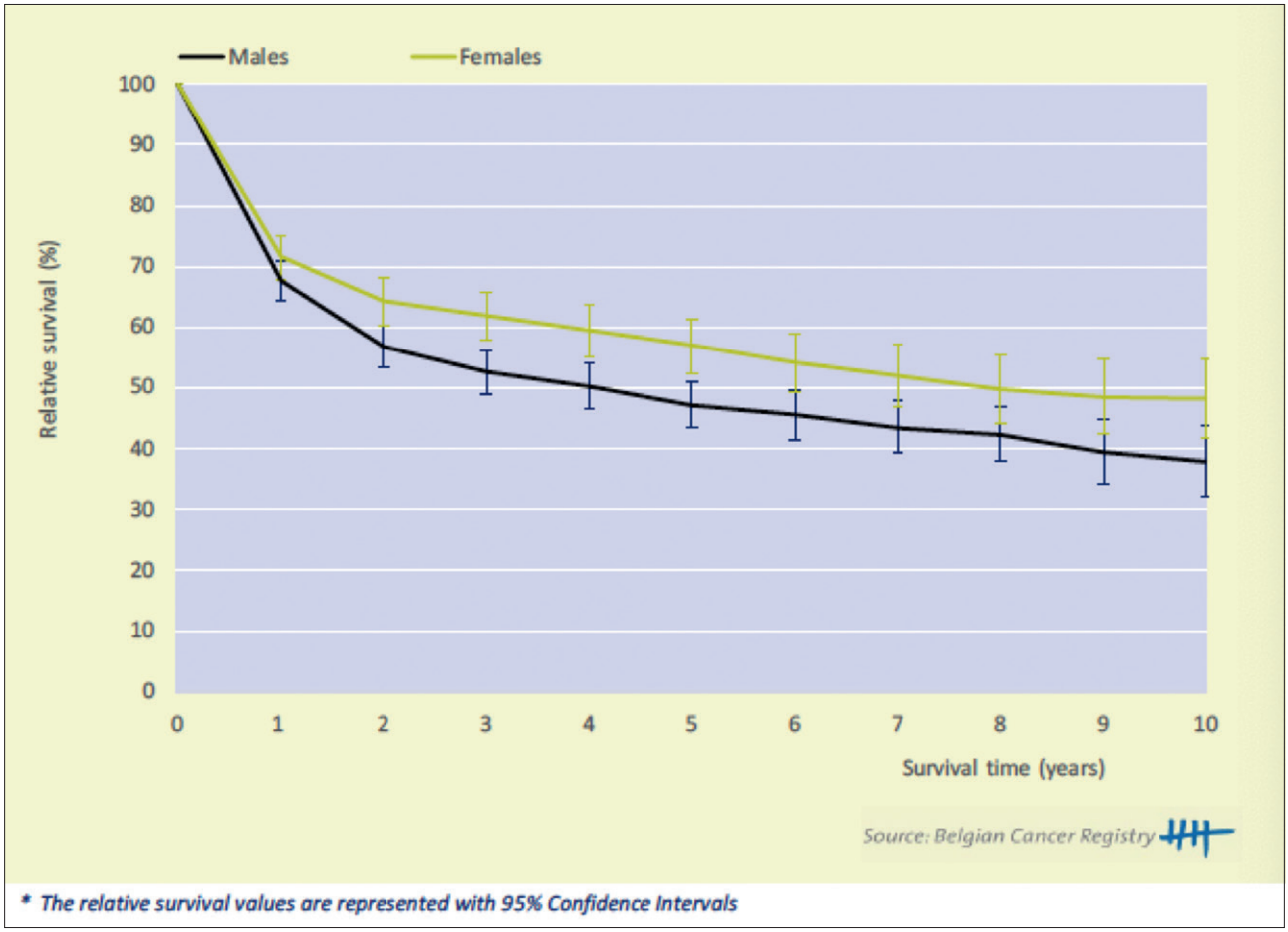

FIGURE 3. Updated relative survival* by sex Belgium 2013-2018.[15]

TABLE 10. Belgian guidelines for transplant in lymphoma.[43]

T-cell lymphoma	Autologous SCT	Allogeneic SCT
PTCL, NOS / AITL / ALK - ALCL		
CR1/PR1	CO/II	NGR/II
Primary refractory (Ch-R)	NGR/II	CO/II
First relapse	SC (if no prior ASCT and Ch-S)/II	CO/II
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II
ALK + ALCL		
CR1/PR1	CO if high-risk disease/II	NGR/III
Primary refractory (Ch-R)	NGR/II	CO/II
First relapse	SC (if no prior ASCT and Ch-S)/II	CO/II
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II
ENKTL		
CR1/PR1	NGR in limited - CO in advanced/II	NGR/III
Primary refractory (Ch-R)	NGR/II	CO/II
First relapse	SC (if Ch-S)/II	CO/II
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II

SCT: stem cell transplantation, PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified, AITL: angioimmunoblastic T-cell lymphoma, ALK: anaplastic lymphoma kinase, ALCL: anaplastic large cell lymphoma, CR1: first complete response, PR1: first partial response, Ch-R: chemo-resistant, CO: clinical option, NGR: not generally recommended, SC: standard of care, ASCT: autologous stem cell transplantation, Ch-S: chemo-sensitive, ENKTL: extra-nodal NK/T-cell lymphoma.

lymphoma.[34] A total of 452 patients, as predefined predominantly with the systemic anaplastic large cell lymphoma subtype (70%), were accrued. The primary endpoint was median progression-free survival (48,2 months for BV+CHP and 20,8 months for CHOP). The study also showed a significant overall survival benefit. Furthermore, the improvement in efficacy of BV CHP was not offset by any apparent increase in toxicity, which has been a limiting factor in previous studies incorporating novel drugs with a CHOP backbone.[35] As of April 2021, brentuximab vedotin is now reimbursed in front line in ALK negative and high-risk ALK positive (with IPI of two or more) ALCL. Based on the pre-specified sub analysis, data were thought not to be strong enough to expand reimbursement in Belgium for other subtypes. There is also no medical need programme for other subtypes.

Surpassing CHOP through the addition of novel drugs to the CHOP backbone has proven challenging data for Etoposide and Brentuximab Vedotin in some subgroup of PTCL. Moreover, the rarity of peripheral T-cell lymphoma has been a substantial barrier to the successful conduction of prospective trials.

OTHERS

Others association as CHOP + alemtuzumab or CHOP + lenalidomide failed to show an advantage compared to CHOP.[36,37]

More recently, the addition of romidepsin to CHOP did not improve PFS, and response rates and OS appeared similar with the combination.[38]

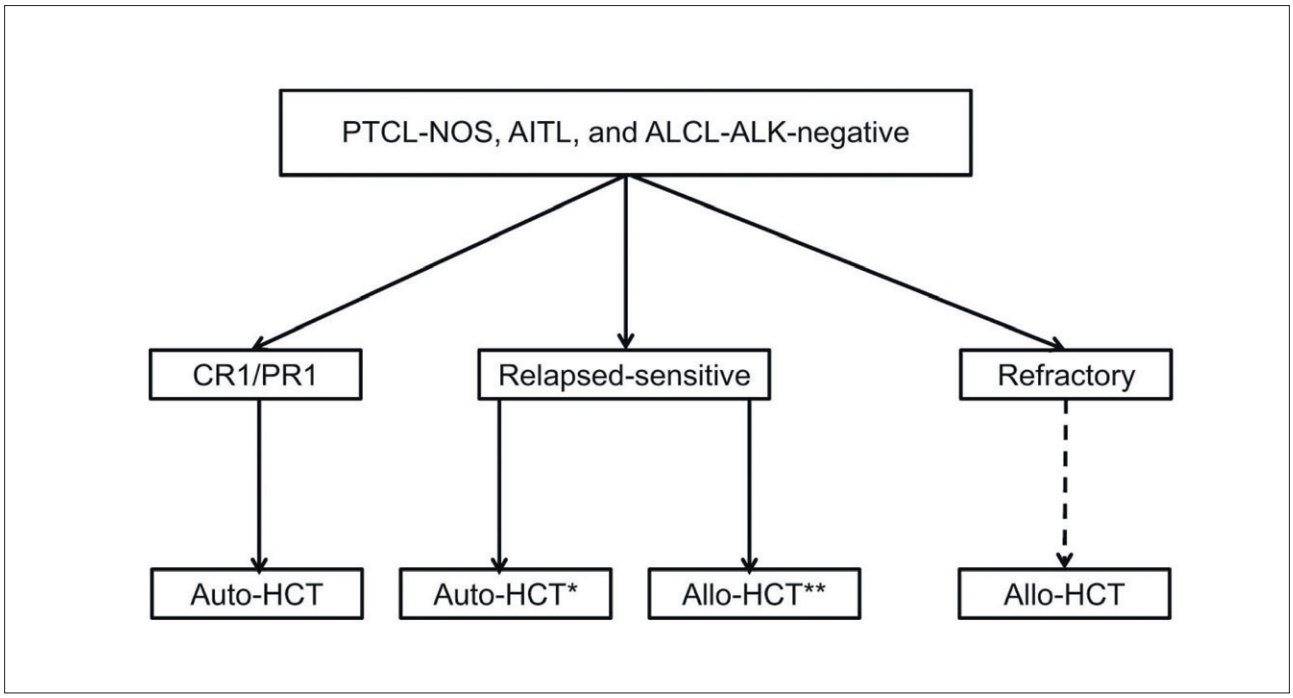

FIGURE 4. Indications of HCT.

A positive phase II study was published by *Falchi et al.* and showed that combined oral 5-azacytidine and romidepsin are effective in patients who were treatment naïve or who had R/R PTCL. Among the 25 enrolled patients, the ORR and complete response rates were 61% and 48%, respectively. However, patients with T-follicular helper cell (TFH) phenotype exhibited higher ORR (80%) and complete remission rate (67%).[39]

RADIOTHERAPY

PTCLs seem to be somewhat less radiosensitive than the aggressive B-cell lymphomas, and higher radiation doses may be needed, although still lower than for most solid tumours. Most types of PTCLs usually present with advanced disease. The few patients with localised disease may be treated with local radiotherapy after chemotherapy, although no randomised evidence regarding this approach exists. Recommended doses are 30-40 Gy.[40] Palliative radiotherapy may be used to treat locally symptomatic disease. Usual palliative doses of 30 Gy in 10 fractions may be used.

ROLE OF AUTOLOGOUS STEM CELL TRANSPLANTATION

The place of autologous stem-cell transplantation (ASCT) as a consolidation procedure for first-line patients achieving a partial or complete response is still highly debated. There are no randomised studies available due to very low frequency of PTCL. Several retrospective and prospective, single-arm phase II trials have reported encouraging results. The recent report from COMPLETE, a prospective, multicentre cohort study showed that ASCT was associated with superior survival for patients with advanced-stage disease or intermediate-to-high International Prognostic Index scores. ASCT significantly improved overall and progression-free survival for patients with AITL but not for patients with other PTCL subtypes. In a multivariable analysis, ASCT was independently associated with improved survival.[41] These data should be interpreted with caution. Only 213 of the 499 included patients were eligible for analysis because of CR. Attention should be paid to the large drop out and the most important struggle of primary refractory PTCL patients that cannot be rescued by autologous. On the contrary, a large multicentric retrospective study from LYSA group did not support the use of ASCT. Neither the Cox multivariate model nor the propensity score analysis found a survival advantage in favour of ASCT.[42]

TRANSCRIPT, a French prospective multicentric phase III study will be proposed shortly by E. Bachy and R. Gressin to answer this difficult question.

ROLE OF ALLOGRAFT STEM CELL TRANSPLANTATION (PROTOCOL AATT)

AATT protocol was the only study that randomise auto-HCT *vs.* allo-HCT for all stages and IPI except stage I and

TABLE 11. Selected experiences with approved single-agents and off-label compounds in PTCL patients.

Molecules	Subtype	ORR	References
Standard (DHAP/ICE etc.)	PTCL (all)	<60%	
Alemtuzumab	PTCL (all)	36%	Enblad, 2004[45]
Alisertib	PTCL	33%	O'Connor, 2019[46]
Azacitidine	AITL	75%	Lemonnier, 2018[47]
Azacitidine + Romidepsin	PTCL	73%	O'Connor, 2019[48]
Belinostat	PTCL (all)	26%	O'Connor, 2015[49]
Bendamustine	PTCL (all)	55%	Damaj, 2012[50]
Brentuximab	ALCL	86%	Pro, 2012[51]
Brentuximab	PTCL (nos/aitl)	41%	Horwitz, 2014[34]
Cerdulatinib	PTCL	43%	Horwitz, 2018[52]
Crizotinib	ALCL ALK+	90%	Passerini, 2014[53]
Cyclosporine	AITL	86%	Ohmoto, 2019[54]
Duvelisib	PTCL (all)	53%	Flinn, 2014[55]
Gemcitabine	PTCL/CTCL	55%	Zinzani, 2010[56]
GDP	PTCL nos	64%	Qi, 2017[57]
Lenalidomide	PTCL (all)	26%	Toumishey, 2015[58]
Mogamulizumab	PTCL (all)	34%	Ogura, 2014[59]
Pralatrexate	PTCL (all)	29%	O'Connor, 2011[60]
Pembrolizumab	PTCL (all)	33%	Barta, 2019[61]
Romidepsin	PTCL (all)	25%	Coiffier, 2014[62]

aaIPI 0 PTCL (*unpublished data: Tournihac, Lugano 2019*). One third of randomised patients could not proceed to auto- or allo SCT mostly because of refractory disease or early relapse. No significant difference for EFS, PFS or OS was found between auto and allo-SCT. Auto-SCT arm showed lower toxicity but more relapses and allo-SCT best tumour control counterbalanced by transplant-related morbidity and mortality.

Despite the lack of evidence from randomised controlled trials, allo-HCT in the upfront setting should not be offered as front-line consolidation for PTCL but is commonly proposed for ATLL (acute and lymphoma type), hepatosplenic lymphoma, and other disorders in which auto-HCT has shown limited or questionable benefit.

Indications of HCT are summarised in the *Figure 4*.

SALVAGE THERAPY

As previously discussed, durable remissions are uncommon with anthracycline-containing regimens, particularly in patients with high-risk disease; moreover, autoSCT cannot be performed in a significant proportion of patients, mainly because they do not achieve an adequate response or progress early. PTCL patients with recurrent disease display a dismal prognosis. A study in 153 relapsed

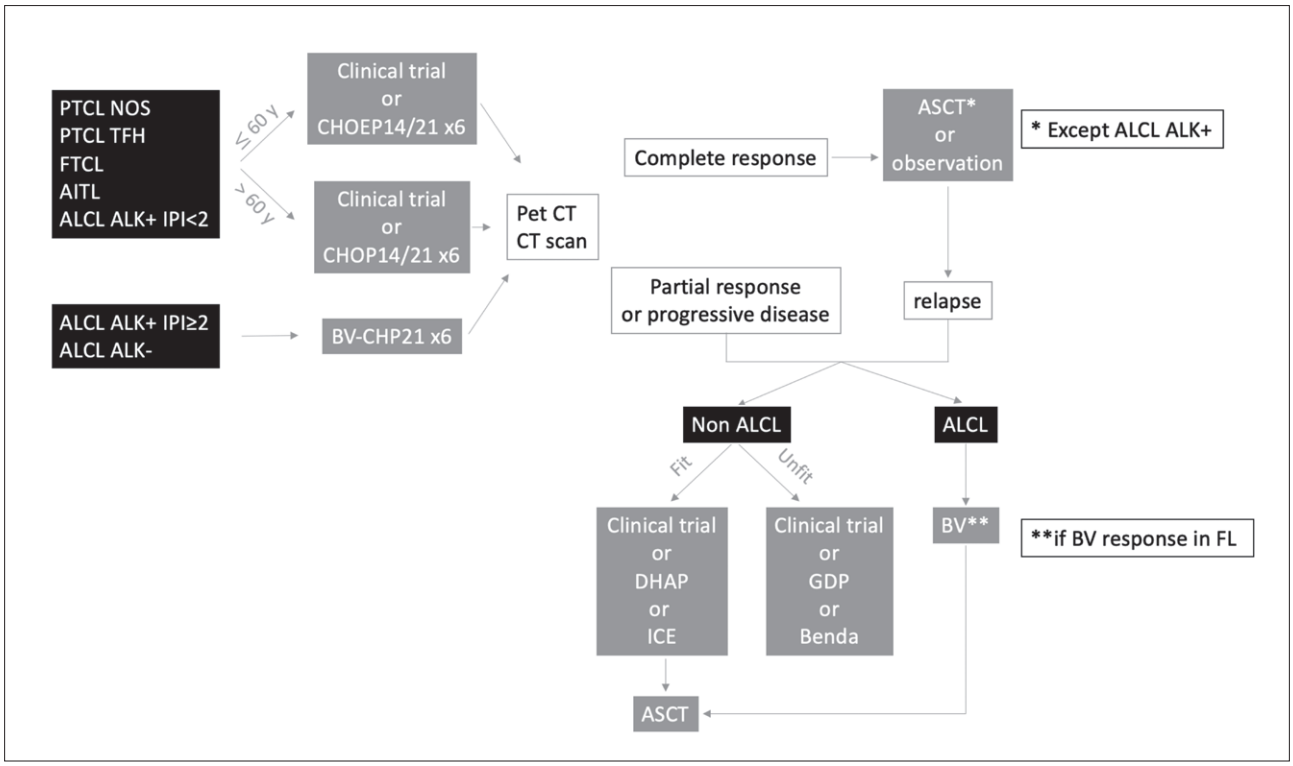

FIGURE 5. Final diagram of treatment guidelines of the BHS.

and refractory PTCL patients, who were not candidates for auto-SCT, documented a median OS and PFS after relapse of 5.5 and 3.1 months, respectively.[44]

PROPOSITION OF THERAPY

Combination chemotherapy (ifosfamide-, platin-, or cytarabine-containing regimens) is sometimes used in younger and fitter patients, mostly as a bridge to auto-SCT or allogeneic transplantation (allo-SCT). However, responses are rarely seen in more than half of cases, response duration is short, and CR is occasional. Gemcitabine and bendamustine, used as single agent, has shown evidence of efficacy in PTCL patients. Four next-generation drugs (pralatrexate, romidepsin, brentuximab vedotin, and belinostat) have recently been approved by the Food and Drug Administration for the treatment of relapsed and refractory PTCL. Approvals were based on response rates alone because none of these drugs has shown an increased OS; for this reason, European approvals of both pralatrexate and romidepsin have been rejected because of a lack of evident clinical benefit. Belinostat is not licensed in Europe, although it has been granted orphan designation status by the European Medicines agency. Brentuximab vedotin is solely approved for the treatment of relapsed or refractory systemic ALCL but seems to be effective in other CD30 + lymphomas. Others drugs as kinase inhibitors (Duvelisib and Alisertib) are displaying relevant activity in PTCL patients. All these drugs are presented in the *Table 11*.

In Belgium, the only new molecule reimbursed is brentuximab vedotin in the specific case of refractory/relapsed anaplastic T-cell lymphoma. The lack of access to the innovative molecules in T-cell lymphomas is flagrant, and medical programme as MNP or CU are urgently needed.

CONSOLIDATION HCT

Auto-HCT should be performed in relapse if it has not been done in first line and if the disease is in is chemosensitive. Allo-SCT is a valid treatment option in transplant-eligible relapsed PTCL patients, after a failed prior autograft of refractory disease. The benefit is most evident in chemosensitive patients. A RIC-allo-SCT should be preferred to a myeloablative approach in order to reduce NRM.[63] A proposition of the place of HCT is presented by the *Figure 4*.[63]

CNS PROPHYLAXIS AND CNS RELAPSES

There is no consensus regarding the indication for CNS prophylaxis. CNS relapse in patients with PTCL is a rare event (2-6%) but the risk varies by subtype.[64,65] ALK+ ALCL patients with extranodal involvement >1 site have a very high-risk of early CNS relapse, and thus evaluation

KEY MESSAGES FOR CLINICAL PRACTICE

1 **Classification of mature T and NK neoplasms is based on the 2016 WHO classification.**

2 **Molecular profiling of tumours has therapeutic and prognostic significance and should be performed for all patients to better tailor therapy.**

3 **Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP21 or 14) based therapy, remains the gold standard for upfront treatment for most subtypes of nodal PTCL. Integration of etoposide may improve results for ALK-positive ALCL. BV-CHP is now reimbursed in Belgium in front line for ALK negative and high risk ALK positive (with IPI of two or more) ALCL but should be extended for all CD30+ PTCL subtypes.**

4 **The use of novel agents as part of upfront therapy should be further explored in larger trials.**

5 **Upfront autologous stem cell transplant in patients in first complete response could be considered excepted for ALCL ALK positive with low IPI.**

6 **Patients with relapsed/refractory PTCL had dismal prognosis and should be treated within the context of a clinical trial when possible.**

of CNS involvement at the time of diagnosis and possible CNS-directed prophylaxis may be considered.[66] The poor outcomes in CNS relapse (one to seven months) are largely driven by systemic rather than CNS disease.

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