Treatment of peripheral T-cell lymphomas: recommendations of the Belgian Hematological Society (BHS)

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The sub-committee on lymphoproliferative disorders of the Belgian Hematological Society has met several times to prepare guidelines on the management of patients with peripheral T-cell lymphomas. Each panellist's expert provided interpretation of the evidence, based on literature review and personal experience. The available evidence was systematically discussed prior to formulating recommendations. A systematic approach to obtain consensus of expert opinion was used. After each meeting, the draft guideline was circulated to all experts for comment and approval. The present guidelines focus on general management of peripheral T-cell lymphomas with special emphasis on more specific disease-adapted strategies.
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Diagnosis, classification, prognosis, fluorodeoxyglucose (FDG) avidity

T-cell lymphomas are divided into precursor T-cell (lymphoblastic) neoplasms, and mature post-thymic lymphomas. The latter are designated as peripheral T -cell lymphomas (PTCLs). PTCLs are highly diverse, reflecting the different cells from which they originate. These include cells from T-cell receptor (TCR) α/β, or TCRγ/lineages, and may have features of cytotoxic, helper, or suppressor lymphocytes, or may present with an aberrant phenotype. PTCLs also include neoplasms of natural killer (NK) cell origin because of the phenotypic and functional properties shared by some cytotoxic T cells and NK cells, with the fundamental difference being that the configuration of the TCR gene is germline in NK cell neoplasms. This is why, in the World Health Organization (WHO) classification of T-cell neoplasms, PTCLs are grouped under the designation "Mature T and NK cell neoplasms" (*Table 1*).[1]

The diagnosis of PTCL relies on a multiparametric methodology combining clinical, pathological, immunophenotypic, and genetic parameters. Detailing this complex approach is beyond the scope of the present recommendations. It is highly recommended to have the diagnosis reviewed by an experienced pathologist. Some entities are well defined, while others lack a distinct profile and are put into a wastepaper basket category called PTCL 'not otherwise specified' (NOS), in analogy of its B-cell counterpart diffuse large B-cell lymphoma (DLBCL), NOS. Because of the lack of dis-

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Table 1. Comparison of simplified WHO 2001 & 2008 classifications of T- and NK cell neoplasms (leukemic/disseminated variants not displayed)

WHO 2001	WHO 2008
Extranodal	
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma (ENKTL), nasal type
Enteropathy-type T-cell lymphoma	Enteropathy-associated T-cell lymphoma (EATL)
Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma (HSTL)
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) (α/β subtype only)
Cutaneous	
Mycosis fungoides	Mycosis fungoides (MF)
Sézary syndrome	Sézary syndrome (SS)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorders	Primary cutaneous CD30-positive T-cell lymphoproliferative disorders • Primary cutaneous anaplastic large cell lymphoma • Lymphomatoid papulosis*
Primary cutaneous anaplastic large cell lymphoma	
Lymphomatoid papulosis*	Borderline lesions
Borderline lesions	**Primary cutaneous peripheral T-cell lymphomas, rare subtypes** **• gamma-delta T-cell lymphoma** ***• CD8 aggressive epidermotropic T-cell lymphoma*** ***• CD4+ small/medium T-cell lymphoma***
Nodal	
Peripheral T-cell lymphoma, unspecified	Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
Angioimmunoblastic T-cell lymphoma	Angioimmunoblastic T-cell lymphoma (AITL)
Anaplastic large cell lymphoma	**Anaplastic large cell lymphoma (ALCL), ALK+**
	Anaplastic large cell lymphoma (ALCL), ALK-

*New distinct categories are shown in bold; provisional categories in bold italics. * Not considered as a neoplastic lesion*

tinct profile, the clinical features and anatomic location of PTCLs are critical in defining entities. Consequently, PTCLs are listed according to their presentation as leukaemic/disseminated, predominantly extranodal, cutaneous, or predominantly nodal diseases (the latter being the most frequent presentation in Europe), taking into account that there is frequent overlap. The 2001 WHO classification for PTCLs was updated in 2008. The new classification expanded some existing disease types and added several new provisional categories (*Table 1*). The most common subtypes in the European Union are PTCL-NOS (up to 34%), angioimmunoblastic T-cell lymphoma (AILT) (29%), and anaplastic large cell lymphoma (ALCL) (9%), with clear disparities with North America (AILT less frequent) and Asia (more frequent NK/T-cell lymphomas and adult T-cell leukaemia/lymphoma (ATLL)).[2] In the present guidelines, mature T -cell leukaemia's (T-cell prolymphocytic leukaemia (PLL), ATLL, aggressive NK cell leukaemia and chronic lymphoproliferative disorders of NK cells) will not be reviewed.

PTCLs are rare tumours (5-20% of all non-Hodgkin's lymphoma (NHL) worldwide), and the majority of them have an inferior prognosis compared to their B-cell counterpart even in the pre-rituximab era.[3] The International PTCL Project has recently reported a five year overall survival (OS) and five year failure-free survival (FFS) of only 32% and 20% respectively, in patients

with PTCL-NOS. Prognosis is predicted by international prognostic index (IPI) (five year OS in patients with IPI four or five was only 11%), and by prognostic index for T-cell lymphoma (PIT), a more recent T-cell-specific prognostic score which includes three characteristics of the IPI (age, performance status (PS), lactate dehydrogenase (LDH)) and bone marrow (BM) involvement.[4] Although these scores are recommended, a majority of patients with PTCL have advanced disease at presentation, which limits their usefulness. In addition, some subtypes have a poor prognosis even in the case of low IPI, such as enteropathy-associated T-cell lymphoma (EATL) and NK/TCL.[2,4,5] Among PTCLs, those in which TCR /δ cells are expressed are extremely aggressive, irrespective of their site of origin. In addition, PTCLs can be associated with hemophagocytic syndrome (HPS), which is sometimes the major determinant of the clinical presentation. HPS can be linked to the production by neoplastic T-cells of cytokines and chemokines.[6] Many biological factors (expression of cytotoxic molecules, Ki-67, chromosomal aberrations, gene expression profile, etc.) have been shown to have prognostic significance, but there is no uniform biological model for prediction of outcome.[7]

The role of fluorodeoxyglucose positron emission tomography (FDG-PET) in significantly altering clinical stage or treatment recommendations in PTCL is unclear.[8,9] FDG-avidity in PTCLs seems less predictable than in B -cell lymphomas. FDG positivity is high in PTCL-NOS, extranodal NK/T-cell lymphoma (ENKL), or AILT for nodal and extra-nodal lesions (sensitivity 95%). However, the results are disappointing for patients with cutaneous laesions as in mycosis fungoides/Sézary syndrome (MF/SS) or cutaneous anaplastic large cell lymphoma (ALCL) (sensitivity 13%).[10] The role of interim evaluation is also controversial since investigators from the Groupe Ouest-Est des Leucémies Aiguës et des Maladies du Sang (GOELAMS) found that a negative interim or post-therapy FDG-PET does not translate into an improved progression-free survival (PFS) in ALK-T/NK lymphomas.[11] Still, PET scanning might aid radiotherapy planning in ENKL.[12]

Primary chemotherapy of PTCL

This section reviews the general approach to most nodal and non-cutaneous extranodal PTCLs. This approach mirrors that of DLBCL, and is mainly CHOP-based (cyclophosphamide, doxorubicin, vincristine en prednisone). Importantly, some of the latter entities might be managed with alternative strategies, and this will be reviewed in the section "Treatment adaptation for specific subtypes of PTCL", which also encompasses some of the cutaneous variants of PTCLs. As stated above, CHOP is the most widely used regimen in PTCL, although it has failed to induce sustained remission in most patients.[3-5,13,14] Any role of anthracycline is even questioned in non-ALK+ PTCLs.[2] CHOP achieves a complete response (CR) rate around 50%, and a five year OS around 30%. Dose-intensified CHOP-based regimens have been explored in PTCL in order to overcome this high rate of failure, and some of them have provided encouraging results in phase II trials. The Groupe d'étude des lymphomes de l'adulte (GELA) reported that an intensive therapy with ACVBP (adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone) was superior to CHOP with regard to both event-free survival (EFS) and OS in high-risk patients with NHL aged from 61 to 69 years. However, T-cell histologies represented less than 20% of the patients included in the latter study. In retrospective subset analysis of T-cell lymphomas included in GELA LNH87, LNH93, and LNH98 protocols, no difference could be seen between CHOP and more intensified strategies across various risk categories.[15] A retrospective analysis from the MD Anderson Cancer Centre did not show a benefit from more intensive therapies as compared to CHOP.[16] The GOELAMS compared VIP (etoposide, ifosfamide, cisplatin)/ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) to standard CHOP and found equal dismal prognosis.[17] The German Non-Hodgkin's Lymphoma Group (DSHNHL) did not find a benefit from shortening the interval (CHOP14) in elderly patients (too few young patients), nor from the addition of etoposide (CHOEP). However, improved EFS (not OS) was seen after the addition of etoposide in a restricted category of low-risk young patients with normal LDH (n=144), especially when ALK+ ALCL were considered.[18] Investigators from Japan have reported an encouraging five year PFS of 61% in 84 patients with PTCL treated in a phase II study with cycloBEAP, a schedule combining doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin and prednisolone, given on alternating weeks for twelve weeks.[19] From these reports (mainly phase II non randomised studies), it has not been demonstrated that natural history of PTCL is affected by increasing the dose of cyclophosphamide or doxorubicin, with less than 30% of patients being cured by anthracycline-containing regimens. These conclusions appear to apply to regimens classically

active in B-cell NHL such as HyperCVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone)[16], Burkitt-type regimen COPADM (cyclophosphamide, vincristine, prednisolone, doxorubicin, méthotrexate)/CYVE (cytarabine, etoposide) or ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin).[20] Gemcitabine-containing regimens, such as GEM-P (gemcitabine with cisplatin and methylprednisolone), PEGS (cisplatin, etoposide, gemcitabine and solu-medrol), or GIFOX (gemcitabine, ifosfamide and oxaliplatin), have been reported, including in upfront treatment, with encouraging response rate, and survival analysis that needs further maturation.[21,22]

Role of radiotherapy

The place of radiotherapy in a disease which is frequently disseminated is limited. Weisenburger et al have recently shown that OS in patients with stage I PTCL-NOS who received initial radiation therapy in addition to chemotherapy was better compared to those who received only chemotherapy, taking into account that this analysis was performed on a restricted number of patients (n=36).[4] In the National Comprehensive Cancer Network (NCCN) guidelines of treatment of PTCLs, radiotherapy at the dose of 30-40 Gy remains an option after CHOP in localised AKL+ ALCL, and more generally after four to six cycles of multi-agent chemotherapy in stage I/II PTCLs with low or low/intermediate IPI.

Role of stem cell transplantation

There are no phase III studies proving that high dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) influences the outcome of patients with PTCL. Most of the reports are phase II studies, often retrospective, with heterogeneous patients (including ALCL ALK+ or without ALK status definition) and selection biases.[21] The DSHNHL has shed some doubt on the expectation that HDT/ASCT will improve results by showing disappointing three year EFS after megaCHOEP and repeated ASCT.[23] Actually, younger patients with T-cell lymphoma and age-adjusted IPI two or three treated on the MegaCHOEP programme did worse (three year EFS 31,6%) than those given eight courses of CHOEP-14 (three year EFS 57,9%). A characteristic of the MegaCHOEP programme that should be emphasised is that, in order to deliver high doses of active drugs as early as possible, the induction period before ASCT was extremely short (only one to three cycles of MegaCHOEP). Mounier et al also showed in a retrospective matched pair analysis that ASCT did not benefit non-anaplastic T-cell NHL.[24] More encouragingly, the Nordic lymphoma group reported a five year OS of 50% after CHOEP-14 x 6 followed by BEAM (BCNU, etoposide, cytarabine, melphalan)/ASCT in responding patients. Interestingly, patients with ALK- ALCL appeared to particularly benefit from this strategy.[25] Corradini et al estimated a twelve year OS of 34% in PTCLs treated upfront with HDT/ASCT. OS was significantly better among patients with ALCL ALK+ compared to the other PTCLs. They also showed that almost 30% of patients could not proceed to ASCT because of disease progression, and that achievement of CR prior to transplantation is a strong predictor of better survival.[26] Overall, only patients in first CR might benefit from ASCT, while patients receiving ASCT in second remission or refractory disease have a poor prognosis. A Belgian consensus on the role of ASCT in PTCL in first line could not be reached. This is why the recommendation to transplant in first line is graded as 2B. Noteworthy, in the on-going ACT-1 trial of the Nordic lymphoma group, ASCT is considered as a standard strategy in both randomisation arms.

Data are limited regarding the use of allogeneic transplantation in PTCL, especially in the frontline setting. The Société Française de Greffe de Moelle et de Thérapie Cellulaire has conducted a retrospective analysis of 77 patients with PTCL (including eight ALCL ALK+, and thirteen ALCL without ALK status definition) who underwent allogeneic transplantation, most of them with total body irradiation (TBI)-based myeloablative conditioning. Although a disease-free plateau was observed (five year OS 57%), five year treatment-related mortality (TRM) was 33%. Interestingly, they showed that disease status at transplantation strongly influenced outcome (five year OS for CR/PR patients 69% versus 29% for SD/PD).[27] Corradini et al have shown that reduced intensity conditioning (RIC) followed by allogeneic SCT is feasible, with low TRM, in relapsing patients. They also show arguments for graft-versus-lymphoma (GVL) effect (long-lasting response to donor lymphocyte infusion (DLI)).[28] More recently, the same group confirmed these data on the evidence of GVL effect and potentially curative role of this strategy with an estimated five year non relapse mortality of 12% and a cumulative incidence of acute (grade II-IV) and chronic GVH of 22% and 27%, respectively.[29] Interestingly, a single-institution retrospective study indicated that outcomes for ASCT were best when conducted in first remission, and

allogeneic transplantation was better for patients with resistant or relapsed disease.[30] The German high grade NHL study group is currently running the DSHNHL 2006-1A (AATT) protocol in which younger patients with PTCL receive a common induction with four cycles of CHOEP-14 and one cycle of DHAP, and are then randomised between BEAM/ASCT or allogeneic transplantation after FBC (fludarabine 125 mg/m^2, busulfan 12 mg/kg, cyclophosphamide 120 mg/kg). PTCLs stage I with an IPI 0, ALCL ALK+, T-cell lymphoblastic lymphoma, and cutaneous T-cell lymphoma (CTCL) are excluded from this protocol. Such prospective efforts to establish the role of allogeneic transplantation in PTCL are highly needed.

Salvage chemotherapy for relapsed/refractory disease

Strategy in relapsing/refractory PTCLs is again similar to that in relapsing/refractory DLBCL and mainly relies on the use of cisplatin- or gemcitabine-containing regimens in the hope of inducing a response enabling a consolidation with autologous or allogeneic transplantation, if not performed earlier. The place of new drugs (pralatrexate, HDACi, monoclonal antibodies, etc.) in this setting requires further evaluation.

New strategies with CHOP as a backbone

The incorporation of novel agents into CHOP-based regimens is a logical step to proceed since CHOP chemotherapy is unsatisfactory, even when intensified or followed by ASCT. Several monoclonal antibodies and immunoconjugates have been tested in PTCL. Using flow cytometry testing for cell surface expression, the frequency of CD52 expression is high in PTCL-NOS, ATLL and CTCL (less in ALCL and NK/TCL), implying a rational role for alemtuzumab in the treatment of these diseases.[31] Alemtuzumab-CHOP (A-CHOP) or alemtuzumab with dose-adapted (Da)-EPOCH has been explored with an encouraging rate of stable CR, although not clearly correlated with CD52 expression.[32,33] However, this strategy is not advised outside of a clinical trial because redhibitory infectious and malignant toxicities can occur.[34] Even when spacing each course of CHOP every 28 days, and reducing alemtuzumab to a single SC dose of 30 mg, life-threatening complications occur.[35] The combination of alemtuzumab with DHAP was also associated with treatment-related deaths and short-lasting disease control.[36] A currently running large randomised international trial (ACT trial) tests in newly diagnosed systemic PTCL the addition of alemtuzumab to six courses of CHOP-14, followed, in younger patients, by HDT/ASCT. To date, the trial has accrued a total of 131 patients. The first planned interim safety analysis of the ACT-1 trial (young patients) based on the first 51 randomised patients has been recently presented, including patients before and after dose-reduction amendment tapering alemtuzumab dose from 360 mg (30 mg on days one and two of each six CHOP course) to 120 mg (30 mg on day one of CHOP courses one to four). This preliminary report describes an important decrease of serious adverse event (SAE) following dose reduction amendment. Monitoring of EBV viraemia is mandatory after alemtuzumab-containing regimens in PTCL.[37] The data above emphasise the risk of combining standard chemotherapy with immunosuppressive compounds in compromised patients such as in PTCL. CHOP-like regimens in combination with bortezomib appear feasible without clearly increasing the response rate. The combination with denileukin diftitox is also feasible and displays a high rate of response in ALCL and AITL.[38]

New drugs

A number of new drugs are currently under evaluation in PTCL. Among them, pralatrexate, a new folate analog, displays significant individual activity in PTCL, and has been approved as single agent for relapsing/refractory disease by the Food and Drug Administration (FDA).[39] Study of the combination of pralatrexate with gemcitabine is currently on-going. Histone deacetylase inhibitors (HDACi), such as romidepsine, are active in PTCL, and have been FDA-approved in the indication of advanced CTCL.[40] SGN-30, a monoclonal antibody targeting CD30 present in ALCL, is poorly active in PTCL. SGN-35 (brentuximab vedotin), an antibody-drug conjugate combining anti-CD30 with an anti tubulin agent, produces frequent and durable responses in ALCL.[41] HuMax-CD4 is a monoclonal antibody against CD4 which can induce cell killing in tumours with T-helper phenotype.[42]

Other monoclonals tested include anti-CD2, anti-VEGF, and anti-CD25. Nucleoside analogs are another class of drugs active in PTCL (gemcitabine, fludarabine, cladribine, clofarabine, nelarabine, pentostatin, and forodesine). Other drugs potentially active in PTCL include bendamustine and lenalidomide.[43,44] Several new combination studies are currently under way in the hope of improving the activity of CHOP alone in PTCL.[7,21] Most of these drugs are currently not available yet in Belgium, so availability must be checked since this situation may have changed.

Treatment adaptation for specific subtypes of PTCL

Mycosis fungoides (MF), Sézary syndrome (SS), and primary cutaneous CD30+ lymphoproliferative diseases are treated specifically, owing to their favourable prognosis. For nodal and non-cutaneous extranodal PTCLs, restricted literature data indicate that some subtypes (AITL, ALCL ALK+, NK/TCL, EATL, gamma/delta TCLs) might benefit from a treatment approach that differs from a standard CHOP-based strategy.

Mycosis fungoides (MF)

Early aggressive chemotherapy, such as CHOP, does not improve survival of patients with MF and is associated with considerable toxicity and short-lasting responses. A much more conservative approach, adapted to the stage of the disease, is recommended.[45] MF staging is done with a TNM-based classification while other PTCLs are classified according to the Ann Arbor staging system. Patients with only patches or plaques, i.e. stages IA (<10% of body surface area (BSA)) or IB (>10% BSA) should be managed with skin-directed therapies (SDT), such as phototherapy (psoralen plus UVA radiation, or UVB), topical steroids or topical cytostatics (ointments with nitrogen mustards can be particularly effective). If the disease is more extensive, a combination of psoralen plus UVA radiation (PUVA) with interferon-alpha can be considered. Patients with localised tumours can have additional radiotherapy (regression can be observed with low doses such as eight Gy in two fractions), which can be curative in patients with early disease. In patients with more advanced disease (stages IIB: cutaneous tumours, III: generalised erythroderma, or IV: pathologic nodes with or without viscera involvement) and refractory disease, SDT and biologic response modifying agents are preferred over systemic aggressive chemotherapy. The former include interferon-alpha (can be combined with PUVA or bexarotene), HDAC inhibitors (vorinostat), bexarotene, or denileukin diftitox. Other possibilities include low-dose methotrexate, total skin electron beam therapy, gemcitabine, alemtuzumab, liposomal doxorubicin, extracorporeal photopheresis (ECP) in case of circulating T-cell clones. Availability in Belgium of many of the above-mentioned drugs should be verified when needed. Bexarotene is reimbursed in patients with advanced (IIB-IVB) CTCL who cannot get interferon-because of contra-indication, intolerance or treatment failure. A currently on-going EORTC study in Belgium investigates lenalidomide maintenance after debulking with gemcitabine or liposomal doxorubicin. Multiple-agent chemotherapy can only be considered in patients with widespread lymph nodes or visceral involvement, or extensive tumour stage MF. Allogeneic transplantation has been attempted in young patients with refractory MF and SS.

Sézary syndrome (SS)

In SS, SDT are necessary adjuvant treatments, but a systemic approach is required, which is similar to that used in advanced-stage MF. However, in SS and erythrodermic MF with blood involvement, extracorporeal photopheresis (ECP) appears to be particularly effective and is considered as the treatment of choice, and is usually combined with bexarotene or interferon-alpha. Of note is that ECP is not reimbursed in Belgium (on-going procedure). ECP, which induces an overall response rate (ORR) of 30-50%, and a complete response rate (CRR) of 14-25%, is not curative. Treatment of pruritus and of staphylococcal skin super infection driving disease exacerbation, is necessary in SS.[46] Second line treatments in SS include low-dose chlorambucil, low-dose methotrexate (MTX), low-dose alemtuzumab, bexarotene, single-agent chemotherapy (e.g. liposomal doxorubicin), and multi-agent chemotherapy.[45]

Lymphomatoid papulosis (LyP)

It is noteworthy that lymphomatoid papulosis (LyP) can be (in approx. 10-20%) preceded by, associated with, or followed by Hodgkin's lymphoma, mycosis fungoides (MF) or systemic anaplastic large cell lymphoma (ALCL). There is no treatment of LyP that can prevent the development of associated lymphomas. For this reason, a conservative approach is recommended. Refraining from active therapeutic intervention (Watch and wait) is legitimate first-line approach in patients with limited disease. For patients with numerous laesions, phototherapy (PUVA) and low-dose MTX (5-30 mg/week orally or intramuscularly) are the best documented therapies. Maintenance treatment may be required but may be associated with long-term complications. For larger LyP laesions, surgical excision and radiotherapy are potential options. Topical steroids can hasten regression. Interferons and retinoids may be active but are not recommended as first line. Multi-agent chemotherapy should be avoided.[47]

Primary cutaneous CD30+ (c-ALCL)

A complete work up is advised in order to exclude cutaneous manifestation of systemic anaplastic lymphoma kinase (ALK)- ALCL. This tumour has an excellent prog-

nosis. Conservative approach (radiotherapy, surgical excision) is advised. Low-dose MTX can be given in more extensive disease, but the experience is more limited than in LyP.[47]

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) (alpha/beta by definition)

Formerly, two groups of SPTCL were recognised based on the T-cell receptor rearrangement: the α/β and γ/δ subtypes. The latter group has a dismal outcome and has been re-classified as "Primary cutaneous gamma-delta T-cell lymphoma", and should be managed as γ/δ TCL (see below). Conversely, patients with α/β phenotype have an excellent outcome if not associated with hemophagocytic syndrome (HPS) (around 17%, which is less frequent than in γ/δ subtype). The presence of HPS has indeed a strong impact on survival expectancy (five year OS 91% versus 46%) in STPCL α/β.[48] Thus, outcome is highly variable among these patients, not universally aggressive and fatal. Systemic steroids and immunosuppressive agents can be considered first. Radiotherapy is recommended in case of solitary skin laesions. Multi-agent chemotherapy can be considered if progressing or associated with HPS.

Angioimmunoblastic T-cell lymphoma (AITL)

Angioimmunoblastic T-cell lymphoma (AITL) portends a poor prognosis even when treated intensively, even with autologous stem cell transplantation (ASCT).[49] The disease often occurs in elderly patients and is associated with polyadenopathies and frequent systemic symptoms, hypergammaglobulinaemia, autoantibodies, and auto-immune manifestations. Anecdotal reports show activity of single-agent steroids, nucleoside analogs, interferon-alpha, ciclosporin or thalidomide.[50] Responses are also observed in AITL following lenalidomide.[51] There is no indication that any of these therapies can improve outcome, but they might play a role in controlling the disease before chemotherapy or in elderly/compromised patients.

Anaplastic large-cell lymphoma (ALCL)

There are three categories of CD30+ ALCL: systemic ALK+, systemic ALK- and primary cutaneous ALCL (c-ALCL ALK-). Survival in systemic ALK+ ALCL is known to be significantly superior to that in ALK- ALCL. Considering the response rate and survival of patients with ALK+ ALCL, consolidation with ASCT is not recommended if patients achieve a CR. It is not known however if high-dose therapy (HDT) and ASCT should nevertheless be proposed to patients with ALK+ ALCL and high IPI. Paediatric regimens, antibodies targeted to CD30, targeted inhibition of nucleophosmin-anaplastic lymphoma kinase (NPM-ALK), or tumour vaccines are currently being evaluated.[52] Interestingly, vinblastine monotherapy is highly efficient in childhood refractory/relapsed CD30+ ALK+ ALCL and may produce durable remissions. Vinblastine can be given at 6 mg/m^2/week for the total duration of therapy (with steroids during the first weeks), and can serve as a bridge before transplantation. Brugières et al reported in this setting an 83% CR rate. Furthermore, five years after the start of vinblastine, 30% of patients remained in CR, with all but two having stopped their treatment for over two years. Additionally, re-treatment with vinblastine was still efficient in most cases.[53] Patients with ALK- systemic ALCL are usually treated similarly to other PTCLs, although their prognosis might be better than PTCL-NOS.[54]

Extranodal NK/TCL, nasal type

The term nasal-type is used in the WHO classification to describe forms arising both in the nasal cavity and in extra nasal sites. Mainstays of treatment in NK/TCL include radiotherapy, use of L-asparaginase and avoidance of anthracycline-based treatments which are disappointing in this subtype of PTCL. The mechanism of resistance to conventional chemotherapy is not fully understood but could be related to frequent P-gp expression. Several groups have shown that L-asparaginase, which is not affected by multidrug resistance, targets tumour cells, such as NK cells, which are unable to synthesise L-asparagine.[55] Chinese investigators have further shown the clinical activity of L-asparaginase in NK/TCL, later confirmed by other groups in Western patients.[56,57] In case of localised disease (stage I) without any risk factors, radiotherapy at high dose (50-60 Gy) alone results in good outcome.[58] However, because of the risk of distant relapse, a combined modality approach (concurrent or sequential chemoradiation) is often recommended, even in localised disease especially in the presence of risk factors (including age >60, B symptoms, ECOG ≥2, elevated LDH, bone or skin invasion, regional node involvement, high Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) titer, etc.). As an example, the National Comprehensive Cancer Network (NCCN) recommends RT (>50 Gy) for stage I disease either alone or combined with cisplatin- or L-asparaginase-containing regimens. Similarly, Chinese investigators recommend that RT could be sandwiched in between cycles combining L-asparaginase, vincris-

Table 2. Guidelines of the EHS: treatment recommendation for nodal and non-cutaneous extranodal PTCLs

Overall recommendations	Category*
Inclusion in a clinical trial is advised given the disappointing results of standard management	
CHOP-based treatments remain standard[1] • 4-6 cycles consolidated by locoregional RT in localized disease (stages I or II) with IPI 0 or 1 might be an option in highly selected patients • 6-8 cycles +/- RT in advanced disease (stages III, IV) or localized disease with IPI 2 or 3	2A
Consider consolidation with HDT/ASCT in first line if responding patients and in the presence of risk factors[2]	2B
In refractory/relapsing patients, use non cross-resistant (mainly platinum- or gemcitabine-based) regimens[3] and consider patient for ASCT if not performed previously, or allogeneic transplantation, or new drug	2A
In case of allogeneic transplantation, consider RIC because of the toxicity of myeloablative conditioning	2B
CNS prophylaxis: no consensus. Prophylaxis as in DLBCL is an option[4]	2B
Treatment adaptation for specific subtypes of PTCL	
ALK+ ALCL: no consolidative transplantation if patient in remission, consider addition of etoposide to CHOP. Consider monotherapy with vinblastine in relapsing/refractory ALCL, potentially as a bridge to HDT	2A
ALK- ALCL: treatment as PTCL-NOS	2A
AITL: treat as PTCL-NOS. For selected elderly patients with comorbidity, a trial with single corticosteroids or cyclosporin may be considered to improve B-cell-related manifestations	2A
NK/TCL: consider concurrent or sequential radiotherapy and L-asparaginase-containing regimens	2A
EATL: ensure appropriate nutrition and manage risk of intestinal perforation. In highly selected patients, the best approach consists of surgical resection, followed by chemotherapy and ASCT. For chemotherapy, induction with CHOP followed by ifosfamide, etoposide and intermediate dose methotrexate-containing regimen (IVE/MTX), might be an option. Alemtuzumab may be active in the rescue setting	2B
HSTL: upfront allogeneic transplantation might be considered since salvage is almost impossible in these patients because of chemoresistance and poor PS	2B

** Grade of recommendation based on NCCN categories of evidence and consensus*
[1] Potential regimens: CHOP-21, CHOP-14, CHOEP-21, CHOEP-14…
[2] IPI 2 or 3, presence of HPS
[3] DHAP, ESHAP, gemcitabine-containing (GDP, GemOX), ICE, pralatrexate, romidepsin, alemtuzumab, bortezomib…
[4] There are limited data on CNS involvement by PTCL. Despite high relapse rate, PTCL carries a low risk of CNS involvement other than the ATLL subtype. Gurion et al have recently shown that risk factors for CNS involvement in PTCL include >1 extranodal site and high/ intermediate-high IPI. They also suggest that prophylactic intrathecal chemotherapy does not appear to reduce the risk of CNS disease.[67]

Abbreviations: ASCT, autologous stem cell transplantation; HDT, high dose therapy; PS, performance status; RT, radiotherapy

Table 3. NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence (phase III studies), there is uniform consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, but still uniform consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, with no uniform uniform consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, with major disagreement that the intervention is appropriate

Key messages for clinical practice

- **Peripheral T-cell lymphomas encompass a wide range of entities with variable prognosis.**
- **The most common subtypes in the European Union are peripheral T-cell lymphomas -not otherwise specified and angioimmunoblastic T-cell lymphoma.**
- **CHOP-based regimens are recommended in first line but several entities deserve a different approach.**
- **Strategy in relapsing/refractory aggressive peripheral T-cell lymphomas is similar to that in relapsing/refractory aggressive B-cell lymphomas.**

tine and prednisone for stages IE to IIE NK/TCL.[59] For disseminated disease, two potential regimens have recently emerged as interesting options. In patients with refractory/relapsing disease, French investigators have reported that asparaginase-methotrexate-dexamethasone (AspaMetDex) given for three cycles followed by RT for more localised disease, or ASCT after BEAM for advanced disease, or three additional cycles for other responders ineligible for ASCT is effective. They showed excellent activity of this strategy and also that development of anti-asparaginase antibodies increases the risk of progression. They also showed that survival is better when EBV DNA became undetectable.[60] Yamaguchi et al have recently reported the SMILE regimen (consisting of methotrexate, ifosfamide, dexamethasone, etoposide, L-asparaginase) in newly diagnosed patients with encouraging efficacy. Based on patient's condition, two cycles of SMILE were followed by additional cycles, ASCT or allogeneic transplantation.[61]

Enteropathy-associated T-cell lymphoma (EATL)

Enteropathy-associated T-cell lymphoma (EATL) is a primary intestinal (most often small intestine) T-cell lymphoma often associated with coeliac disease (CD), comprising two subtypes (type 1 and type 2) with distinct morphologic and genetic patterns. Prognosis of EATL is poor due to treatment-resistance, risks of intestinal perforation and intra-abdominal sepsis. EATL is usually managed with anthracycline-containing regimens, which might improve OS and FFS compared to other therapies or no therapy.[62] Many other regimens that share two to four cornerstone drugs present in the CHOP schedule have been tried, but with similarly disappointing results and even higher toxicity.[63] More recently, Sieniawski et al reported a pilot regimen IVE/MTX (ifosfamide-vincristine-etoposide/methotrexate) followed by ASCT with five year PFS and OS of 52% and 60% respectively which was superior to historical controls treated with anthracycline-based regimens. Of note, is that the IVE/MTX protocol starts with one cycle of CHOP to minimise the risk of side effects such as perforation, anastomotic breakdown, or wound dehiscence (in the post surgery patient), and to allow a limited recovery period before the more intensive part of the regimen begins. IVE/MTX was well tolerated (MTX was given at intermediate dose of 1,500 mg/m^2).[64] Other interesting agents in EATL include alemtuzumab and cladribine (active in refractory CD).[63]

Given that malnutrition is a common feature, most patients need parenteral nutrition at least initially. The role of surgery lies in debulking, resection of tumour masses with high risk of obstruction or perforation, although there is a risk of delayed chemotherapy in case of post-operative complications. Single case reports indicate that patients who have undergone a complete resection might have a better prognosis and a lower risk of perforation.[63] Strict adherence to gluten-free diet should be maintained and remains the only way to prevent EATL.

Hepatosplenic T-cell lymphoma (HSTCL)

Extranodal lymphoma derived from cytotoxic γ/δ T cells gives an extremely poor outcome because of marked chemoresistance or short-lasting response with CHOP-based therapy, this pattern is frequently seen in HSTCL. HSTCL often presents in the setting of immune system suppression (such as solid organ transplantation). Splenectomy for therapeutic purposes is insufficient but might be considered to improve thrombocytopaenia. Immunosuppression reduction does not appear to be sufficient in this disease.[6] A satisfactory response rate can be observed after induction chemotherapy with CHOP-like regimens, or DHAP (dexamethasone, high-dose cytarabine, cisplatin)/ESHAP, or hyperCVAD, some-

times followed by HDT/ASCT, but long-term disease control remains poor. Many investigators advocate transplantation as first line since salvage is almost impossible in this disease due to poor performance status (PS) and chemoresistance.[21,65] A few cases of patients successfully treated with allogeneic transplant have been reported.[65] Anecdotal activity of pentostatin, cladribine, deoxycoformycin, alemtuzumab, or bortezomib combined with CHOP, have been reported.[66]

Conclusions and overall recommendations of the BHS

Table 2 displays a summary of the BHS general recommendations for treatment of PTCL as well as suggestions for a more tailored approach in some subtypes. *Table 3* shows the NCCN categories of evidence and consensus used to grade the BHS recommendations. In nodal and non-cutaneous extranodal PTCLs, lack of validation in specifically designed prospective phase III studies, fractionated literature, short follow-ups, strategies inspired from B-cell lymphoma, and small cohorts, are obvious limitations to the establishment of guidelines with a strong grading of recommendations for everyday practice. CHOP-derived regimens remain the standard of care, with ASCT as an option in young patients with histologies other than ALK+ ALCL, and high-risk features (such age-adjusted IPI score two or three, or elevated LDH) and response to chemotherapy. A small proportion of patients with localised disease and no risk factors could be treated with chemotherapy followed by involved field radiotherapy. There is no clear indication that allogeneic transplantation should be performed in first line, although this might be an option in patients with high risk of relapse, such as in gamma-delta TCLs, especially when combined with HPS. Overall, inclusion in prospective well-designed trials is highly recommended.

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List of abbreviations

ABVD: adriamycin, bleomycin, vinblastine, dacarbazine **A-CHOP:** alemtuzumab-CHOP **ACVBP:** adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone **ATLL:** adult T-cell leukaemia/lymphoma **AILT:** angioimmunoblastic T-cell lymphoma **ALCL:** anaplastic large cell lymphoma **ASCT:** autologous stem cell transplantation **AspaMetDex:** asparaginase-methotrexate-dexamethasone **ATLL:** adult T-cell leukemia/lymphoma **BEAM:** BCNU, etoposide, cytarabine, and melphalan **BHS:** Belgian Hematological Society **BM:** bone marrow **DLBCL:** diffuse large B-cell lymphoma **c-ALCL:** primary cutaneous anaplastic large cell lymphoma **CD:** celiac disease **CHOP:** cyclophosphamide, doxorubicin, vincristine en prednisone **COPADM:** cyclophosphamide, vincristine, prednisolone, doxorubicin, méthotrexate **CR:** complete response **CTCL:** cutaneous T-cell lymphoma **CYVE:** cytarabine, etoposide **DHAP:** dexamethasone, high-dose cytarabin, cisplatin **DLI:** donor lymphocyte infusion **DSHNHL:** German High Grade Non-Hodgkin's Lymphoma Study Group **EATL:** enteropathy-associated T-cell lymphoma **ECP:** extracorporeal photopheresis **EFS:** event-free survival **ENKL:** extranodal NK/T cell lymphoma **ESHAP:** etoposide, methylprednisolone, cytarabine (high-dose),cisplatin) **GOELAMS:** Groupe Ouest-Est des Leucémies Aigues et des Maladies du Sang **FDA:** food and drug administration **FDG-PET:** fluorodeoxyglucose positron emission tomography **FFS:** failure-free survival **GELA:** *Groupe d'étude des lymphomes de l'adulte* **GEM-P:** gemcitabine, cisplatin, methylprednisolone **GIFOX:** gemcitabine, ifosfamide, and oxaliplatin **GVL:** graft-versus-lymphoma **HDACi:** histone deacetylase inhibitors **HDT:** high-dose therapy **HPS:** hemophagocytic syndrome **HyperCVAD:** fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone **HSTCL:** hepatosplenic TCL **IPI:** international prognostic index **IVE/MTX:** ifosfamide-vincristine-etoposide/methotrexate **LP:** lymphomatoid papulosis **MF:** mycosis fungoides **NCCN:** National Comprehensive Cancer Network **NOS:** not otherwise specified **NPM-ALK:** nucleophosmin-anaplastic lymphoma kinase **OS:** overall survival **PEGS:** cisplatin, etoposide, gemcitabine, solumedrol **PIT:** prognostic index for T-cell lymphoma **PFS:** progression free survival **PTCL:** peripheral T-cell lymphoma **PTCL-NOS:** peripheral T-cell lymphoma, not otherwise specified **PS:** performance status **PUVA:** psoralen plus UVA radiation **RIC:** reduced-intensity conditioning **SAE:** serious adverse event **SDT:** skin-directed therapies **SMILE:** methotrexate, ifosfamide, dexamethasone, etoposide, L-asparaginase **SPTCL:** subcutaneous panniculitis-like T-cell lymphoma **SS:** Sézary syndrome **TBI:** total body irradiation **T-cell PLL:** T-cell prolymphocytic leukemia **TCR:** T-cell receptor **TRM:** treatment-related mortality **VIP:** etoposide, ifosfamide, cisplatin **WHO:** World Health Organization