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Peripheral T- and natural killer-cell lymphomas: ESMO-EHA Clinical Practice Guideline for diagnosis, treatment, and follow-up

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INCIDENCE AND EPIDEMIOLOGY

Peripheral T-cell and natural killer (NK)-cell lymphomas (PTCLs) represent a heterogeneous group of neoplasms derived from post-thymic T- or NK cells, with diverse morphological patterns, phenotypes, and clinical presentations. The International Consensus Classification and World Health Organization (WHO) classification of lymphoid and hematopoietic neoplasms recognize >30 PTCL entities^{1,2} (Supporting Information: Table S1 and Supporting Information Section 1). The incidence and epidemiology of PTCL are described in Supporting Information Section 2. This clinical practice guideline (CPG) covers PTCLs with primary nodal, extranodal, and leukemic presentation. Guidelines for primary cutaneous T-cell lymphomas are reported elsewhere.³

DIAGNOSIS, PATHOLOGY, AND MOLECULAR BIOLOGY

Accurate identification and diagnosis of PTCL is mandatory for adequate clinical management, as treatment should be adapted for each entity. Several entities present with a wide pathological spectrum and there is substantial overlap in morphology, immunophenotype, and mutational landscape between diseases. The differential diagnosis of PTCL is broad and includes various reactive conditions, particularly primary immune deficiencies, inflammation, autoimmune diseases, infections, Hodgkin lymphoma, and, in some instances, B-cell lymphomas.⁴ Overtly malignant PTCLs must be distinguished from the recently recognized indolent clonal T- or NK-cell lymphoproliferative disorders.^{1,2} Given the low prevalence of PTCLs, most pathologists

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have insufficient experience to confidently diagnose them; therefore, diagnosis should be established or confirmed by a hematopathologist with expertise in PTCL who has access to all slides and ≥ 1 representative paraffin block of the biopsy.^{5,6}

Clinicopathological correlation is critical for diagnosis, incorporating imaging findings, symptoms, and laboratory information. Anatomical localization can pre-sort for specific entities (e.g., hepatosplenic T-cell lymphoma [HSTCL], Epstein-Barr virus [EBV]-associated extranodal NK- or T-cell lymphoma [ENKTCL] nasal type, enteropathy-associated T-cell lymphoma [EATL], and breast implant-associated anaplastic large-cell lymphoma [BIA-ALCL]). Autoimmune and inflammatory diseases (e.g., celiac disease and inflammatory bowel disease), immunocompromised status, ethnicity, origin from endemic regions (e.g., within Asia, Africa, or South America for adult T-cell leukemia or lymphoma [ATLL]) or infection (e.g., EBV in tumor cells, human T-cell lymphotropic virus type 1 [HTLV-1]) may further support identification of entities.

Diagnosis should rely on surgical excisional or incisional biopsy whenever possible⁵ to allow adequate histopathological assessment and provide sufficient tissue for immunohistochemistry (IHC) and molecular studies. When surgery is not possible, core needle biopsy or biopsies may be adequate for initial management⁵; however, their accuracy is substantially lower than surgical biopsies for diagnosis and subclassification.^{7,8} Several cores are warranted to anticipate future needs for archived biopsy material. In addition to IHC, flow cytometry has a role in diagnosing and staging PTCL in fluids (blood, ascites, pleural effusion, and cerebrospinal fluid).

The indication of the neoplastic nature of a T-cell population is based on (i) morphology (including overall tissue architecture), atypical cytology and microenvironment features; (ii) aberrant T-cell phenotype; and (iii) presence of a disease-associated genetic alteration, pathogenic mutation(s) or clonally rearranged T-cell receptor (TCR) genes.⁹ Morphological clues, immunophenotypical markers, and genetic molecular studies are summarized in Supporting Information: Tables S2 and S3. Various phenotypic aberrancies occur in PTCLs. Loss or reduced expression of one or more pan-T-cell antigens (cluster of differentiation [CD]2, surface CD3, CD4, CD5, CD7, CD8, and TCR) is common across various entities. Coexpression of CD30 is a defining feature of anaplastic large-cell lymphoma (ALCL), but is also observed in many other entities. Demonstration of differentiation markers related to follicular helper T cells (CD10, B-cell lymphoma 6, programmed cell death protein 1 [PD-1], CXC chemokine ligand 13, inducible T-cell costimulatory) is key for diagnosing follicular helper T-cell-derived lymphoma (TFHL). Cytotoxic markers (cytotoxic granule-associated RNA binding protein, granzyme B, and perforin) are useful for the characterization of extranodal T-cell neoplasms and PTCL not otherwise specified (PTCL-NOS). The latter may be further defined according to the expression of markers of type 1 T helper cells (CXC chemokine receptor 3 and T-box transcription factor 21) and type 2 T helper cells (C-C chemokine receptor type 4 [CCR4] and GATA binding protein 3). FISH is commonly used to assess frequent gene rearrangements or fusions, notably for genetic subtyping of anaplastic lymphoma kinase (ALK)-negative ALCL based on *DUSP22* with or without *TP63* rearrangement. The detection of gene variants may rely on targeted assays for certain hotspots (e.g., *RHOA* p.G17V or *IDH2* p.R172 mutations, which both support a diagnosis of TFHL) but is more commonly achieved by high-throughput sequencing (HTS) of panels of genes. Many of the recurrent aberrations found in PTCLs involve genes related to epigenetic regulation (*TET2*, *DNMT3A*, *IDH2*, *ARID1A*, *SETD2*, and *INO80*), components of the TCR, nuclear factor kappa B and Janus kinase (JAK)-signal transducer, and activator of transcription signaling pathways (*CD28*, *CARD11*, *RHOA*, *PIK3CD*, *PLCG1*, *JAK1*, *JAK3*, *STAT3*, and *STAT5B*) or genes involved in the

regulation of cell cycle and apoptosis (*ATM*, *CDKN2A*, *FAS*, and *TP53*).⁹ HTS complements classical TCR gene rearrangement studies to determine clonality, given that TCR gene-based assays may give false-positive results for non-malignant clones or false-negative polyclonal results in T-cell malignancies. HTS may also assist therapeutic decisions, as some PTCL-associated genetic lesions may support a rationale for subtype-specific intervention.¹⁰ An overview of the main defining features of common PTCL entities is presented in Supporting Information: Table S4. The diagnostic approach to nodal PTCLs is summarized in Supporting Information: Figure S1 and Supporting Information Section 3.

Bone marrow (BM) is often the main tissue source providing conclusive diagnostic documentation in leukemic entities such as T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia (T-LGL), NK-cell large granular lymphocytic leukemia (NK-LGL), aggressive NK-cell leukemia (ANKL), and ATLL. HSTCL is the only non-leukemic PTCL with evidence of BM involvement in almost all cases. BM involvement is characterized by a typical intrasinusoidal lymphoid infiltrate, and its diagnosis often relies on BM biopsy.¹¹ When primary BM diagnosis is required in rare cases of extranodal lymphomas presenting with isolated BM disease, PTCL diagnosis can be particularly challenging.¹²

Recommendations

- Clinicopathological correlation, incorporating imaging findings, symptoms, and laboratory information, should be a mainstay of diagnosis (III, A).
- Diagnosis of PTCL should, whenever possible, rely on a surgical excisional or incisional biopsy (II, A).
- Diagnosis should be based on morphology, aberrant T-cell phenotypes, and the presence of pathogenic mutations, virus infection (EBV or HTLV-1), or TCR clonality (II, A).

STAGING AND RISK ASSESSMENT

Multidisciplinary team (MDT) approach

An MDT approach is preferred, including hematopathologists, diagnostic imaging physicians, hematologist-oncologists, and radiotherapists with expertise in PTCL. MDT evaluation should occur at diagnosis for clinicopathological validation of disease entity, assessment of disease extent, and overall risk profiling and to facilitate a rational, evidence-based treatment strategy, including potential planning of hematopoietic stem-cell transplantation (HSCT). Subsequent MDT evaluations can occur, if needed, at interim and end-of-treatment (EOT) assessments.

Pretreatment laboratory tests

Laboratory tests include complete blood count, flow cytometry of peripheral blood (in primary leukemic entities), blood chemistry (e.g., lactate dehydrogenase [LDH] and uric acid), renal and hepatic function tests, serum immunoglobulins and screening for human immunodeficiency virus, HTLV-1 (in ATLL), hepatitis B, hepatitis C, and EBV.

Diagnostic imaging and BM evaluation

If available, positron emission tomography (PET)-computed tomography (CT) is the preferred imaging modality before treatment, at

first restaging (optional) and EOT.¹³ If PET-CT is not available, diagnostic CT of the neck, chest, abdomen, and pelvis can be used, acknowledging that PTCL often presents with extranodal disease, which may not be adequately imaged by CT. The role of PET-CT in primary leukemic PTCL requires further elucidation, but it is established in acute and lymphoma-type ATLL. While PET-CT is useful for detecting potential residual lesions at EOT, [¹⁸F]2-fluoro-2-deoxy-D-glucose (FDG)-avid lesions are not sufficient for a conclusive diagnosis; therefore, biopsy confirmation is necessary. Nodal PTCLs are virtually all FDG-avid on PET-CT, and additional sites of disease are identified in ≤50% of patients at diagnosis.¹³ Magnetic resonance imaging (MRI) is a useful tool in ENKTCL for an accurate evaluation of sites of disease (e.g., facial skeleton, central nervous system [CNS], and upper aerodigestive tract) and, if applicable, for planning radiotherapy (RT) for involved anatomical structures. Some studies have reported lower sensitivity of PET-CT in identifying BM disease in PTCL compared to Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL).¹⁴ BM aspiration and biopsy should, therefore, be included in staging. BM involvement has been retrospectively reported in 35.8% of nodal PTCLs.¹⁵ BM might disclose associated myeloid disorders¹⁶ given the frequency of underlying clonal hematopoiesis, especially in TFHL.¹⁷

Clinical progression or recurrence of systemic PTCL is not typically associated with histological transformation; however, suspected relapses may represent proliferation of a different lineage (B cell or even myeloid), reactive conditions including granulomatous reactions, or infectious processes, which require different treatments. Rebiopsy, when possible, can guide further therapy. In case of relapse, the most recent biopsy material is preferred for biomarker assessment and identification of potential therapeutic targets.

Prognostic indices

Supporting Information Section 4 provides a summary of prognostic indices in PTCL overall and for specific entities.

Recommendations

- Management of all patients should be discussed by an MDT including hematopathologists (including specialists in pathology, cytology, and molecular biology), diagnostic imaging specialists, hematologist-oncologists, and radiotherapists with specific experience in PTCL (I, A).
- If available, PET-CT at diagnosis, interim (optional) and at EOT can be considered the preferred imaging modality for all nodal and extranodal (non-leukemic) PTCLs (I, B). If PET-CT is not available, diagnostic CT can be used (III, C), although CT detection of extranodal disease may be inadequate in some cases.
- In all cases, a BM biopsy is recommended for accurate staging, including studies of virus expression (I, A).
- Additional tests should be carried out in some entities, such as assessment of peripheral blood cells for immunophenotype (e.g., flow cytometry for primary leukemic entities) and measurement of viral load (e.g., EBV DNA in ENKTCL) (II, A).
- Rebiopsy is recommended at relapse or progression (I, A).

FIRST-LINE TREATMENT

All patients with PTCL should be offered the opportunity to participate in a clinical trial whenever possible. An overview of first-line treatment strategies is shown in Figure 1 (nodal PTCL), Figure 2

(extranodal PTCL), and Figure 3 (leukemic PTCL). Complementary and subtype-specific algorithms can be found in the [Supporting Information](#) as outlined below.

PTCL-NOS and TFHL (angioimmunoblastic and follicular types and NOS)

First-line treatment

Although outcomes are poor, cyclophosphamide-doxorubicin-vincristine-prednisolone (CHOP) remains the standard of care for non-ALCL nodal subtypes. Attempts to replace the CHOP or CHOP-like backbone have not yielded superior results. A detailed algorithm for the first-line management of PTCL-NOS and TFHL is shown in Supporting Information: Figure S2.

Addition of etoposide to CHOP

In a retrospective analysis of 289 patients treated within trials of the German High-Grade Non-Hodgkin Lymphoma Study Group, CHOP-etoposide (CHOEP) was associated with a superior 3-year event-free survival (EFS) rate versus CHOP in patients with ALK-positive ALCL aged <60 years with normal serum LDH and in patients with ALK-negative ALCL, PTCL-NOS, or angioimmunoblastic T-cell lymphoma (AITL) with International Prognostic Index (IPI) score of <1.¹⁸ In the Nordic NLG-T-01 study, 160 patients with PTCL (of which 58% had PTCL-NOS or AITL) received six cycles of CHOEP-14 followed, in responding patients, by autologous HSCT (auto-HSCT).¹⁹ The 5-year overall survival (OS) and progression-free survival (PFS) rates were 51% and 44%, respectively. The trial did not include patients with ALK-positive ALCL. In two real-world data reports from the Swedish Lymphoma Registry, the addition of etoposide to CHOP was associated with improved OS (hazard ratio [HR] 0.38) and PFS in ALK-positive ALCL²⁰ and improved PFS (HR 0.49) in other nodal subtypes and EATL.²¹ A recent population-based cohort study from The Netherlands evaluated CHOEP and consolidative auto-HSCT in 1427 patients with PTCL aged 18–64 years.²² A cohort from the “pre-etoposide and -auto-HSCT era” (1989–2009) was compared to one from the “etoposide and auto-HSCT era” (2009–2018). The risk of lymphoma-related mortality in patients with ALK-positive ALCL was 6.3 times lower for those who received CHOEP than for those who received CHOP. Differences observed in other PTCL subtypes were not significant.

CHOP in combination with novel drugs

In the randomized ECHELON-2 trial, the anti-CD30 antibody-drug conjugate brentuximab vedotin (BV) combined with cyclophosphamide-doxorubicin-prednisolone (CHP) was superior to standard CHOP in ALCL, particularly ALK-positive ALCL.²³ No improvement was observed in PTCL-NOS or TFHL, although the number of patients with these subtypes was limited. BV-CHP is not approved for PTCL-NOS and TFHL in Europe. A small single-arm phase II study of cyclophosphamide-etoposide-vincristine-prednisolone-pralatrexate (CEOP-P) reported modest responses (2-year PFS and OS rates of 39% and 60%, respectively) that were not superior to historical outcomes with CHOP.²⁴ Recent randomized studies evaluating the addition of the anti-CD52 monoclonal antibody alemtuzumab (DSHNHL2006-1B/ACT-2 trial²⁵) or the histone deacetylase inhibitor romidepsin (Ro-CHOP trial²⁶) to CHOP did not demonstrate improved survival. A post hoc exploratory subgroup analysis of Ro-CHOP data, however,

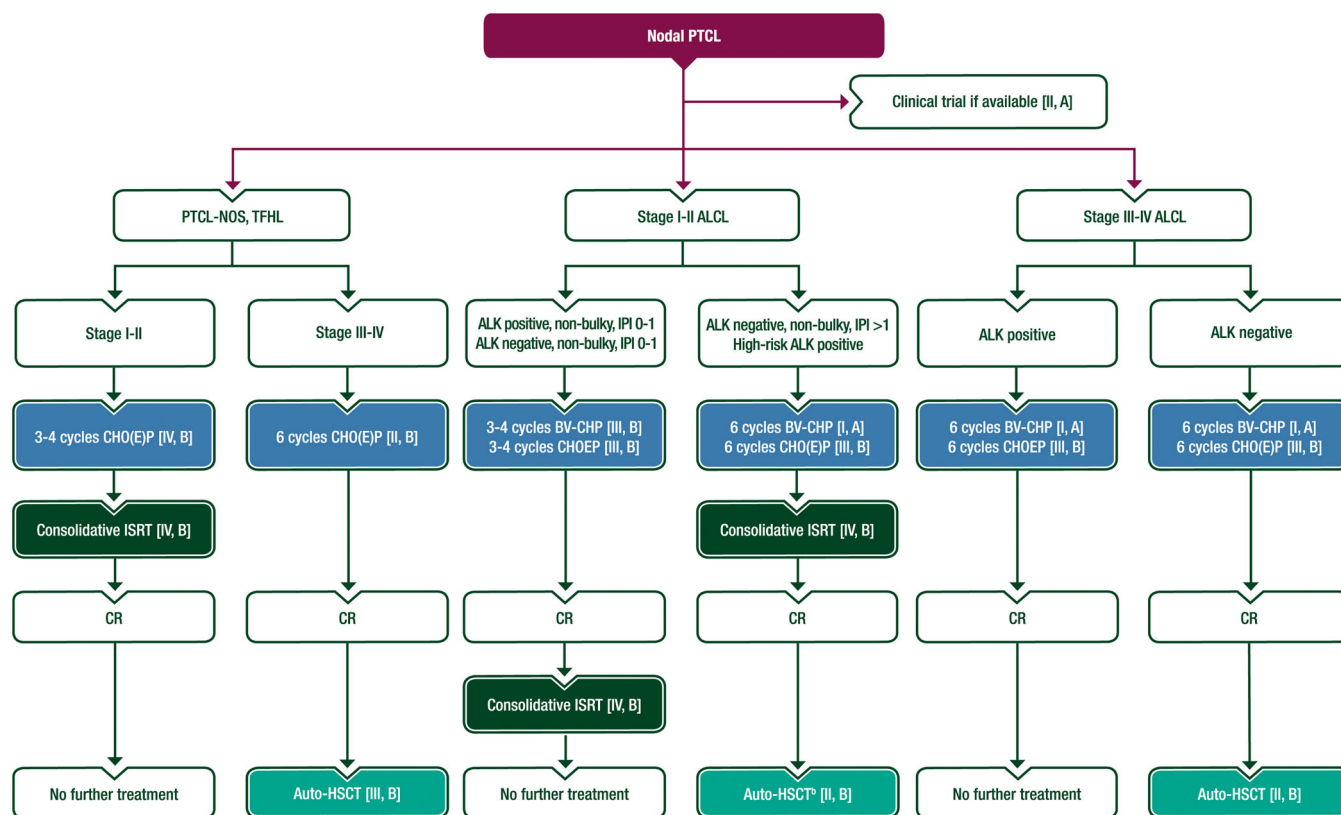


FIGURE 1 Overview of first-line treatment in nodal PTCL.^a Purple: algorithm title; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects. ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; auto-HSCT, autologous hematopoietic stem-cell transplantation; BV-CHP, brentuximab vedotin–cyclophosphamide–doxorubicin–prednisolone; CHOEP, cyclophosphamide–doxorubicin–vincristine–etoposide–prednisolone; CHO(E)P, cyclophosphamide–doxorubicin–vincristine–etoposide–prednisolone; ChT, chemotherapy; CR, complete remission; IPI, International Prognostic Index; ISRT, involved-site radiotherapy; NOS, not otherwise specified; PTCL, peripheral T-cell or natural killer-cell lymphoma; RT, radiotherapy; TFHL, follicular helper T-cell-derived lymphoma. ^aFor subtype-specific treatment algorithms, see Supporting Information: Figures S2 and S3. ^bCan be considered for patients with high-risk ALK-positive ALCL with no CR after three cycles of ChT (III, B).

reported improved outcomes in romidepsin-treated patients with TFHL.²⁷ DSHNHL2006-1B/ACT-2 excluded patients with ALCL (due to lack of CD52 expression in ALCL) and Ro-CHOP excluded patients with ALK-positive ALCL. A recent phase II trial testing the addition of 5-azacitidine (5-aza) to CHOP in 17 patients with newly diagnosed TFHL reported a complete remission (CR) rate of 88.2%.²⁸

Consolidative auto-HSCT in the first response

Prospective^{19,29} and retrospective^{22,30,31} studies have reported favorable outcomes in patients with PTCL undergoing consolidative auto-HSCT in the first response; however, other studies did not replicate this.³² In a randomized phase III study evaluating auto-HSCT versus allogeneic HSCT (allo-HSCT) following anthracycline-based first-line therapy in high-risk nodal PTCL, EFS, and OS outcomes were similar with both treatments.³³ At a median follow-up of 42 months, 3-year EFS rates were 43% for allo-HSCT and 38% for auto-HSCT, and 3-year OS rates were 57% and 70%, respectively. Auto-HSCT was associated with a higher relapse rate (36% vs. 0% with allo-HSCT), while allo-HSCT was associated with higher transplant-related mortality (31% vs. 0% with auto-HSCT). In a Swedish intention-to-treat analysis of real-world data from 252 patients with nodal PTCL (ALK-positive ALCL excluded) or EATL, patients who received consolidative auto-HSCT had improved OS (HR 0.58, $p = 0.004$) and PFS

(HR 0.56; $p = 0.002$) compared to patients who were treated without auto-HSCT.²¹ In a population-based cohort study in The Netherlands, patients across all subtypes undergoing auto-HSCT consolidation had a higher 5-year OS rate than those who did not (81% vs. 39%, respectively, $p < 0.01$), regardless of CR achievement.²² Overall, auto-HSCT is an acceptable option in chemosensitive disease responding to first-line therapy. A randomized study comparing auto-HSCT with observation in patients who achieved CR after first-line treatment is ongoing (NCT05444712; TRANSCRIPT).

Management of limited-stage PTCL

Recent reports suggest that patients with low-risk, limited-stage nodal PTCL have similar outcomes regardless of whether they receive abbreviated chemotherapy (ChT) (e.g., three to four cycles) plus involved-site RT (ISRT) or a full ChT course (e.g., six cycles).^{34–36}

ALCL, systemic types

Limited stage

Most patients with ALCL present with advanced-stage nodal disease; however, extranodal involvement can occur, often involving bone,

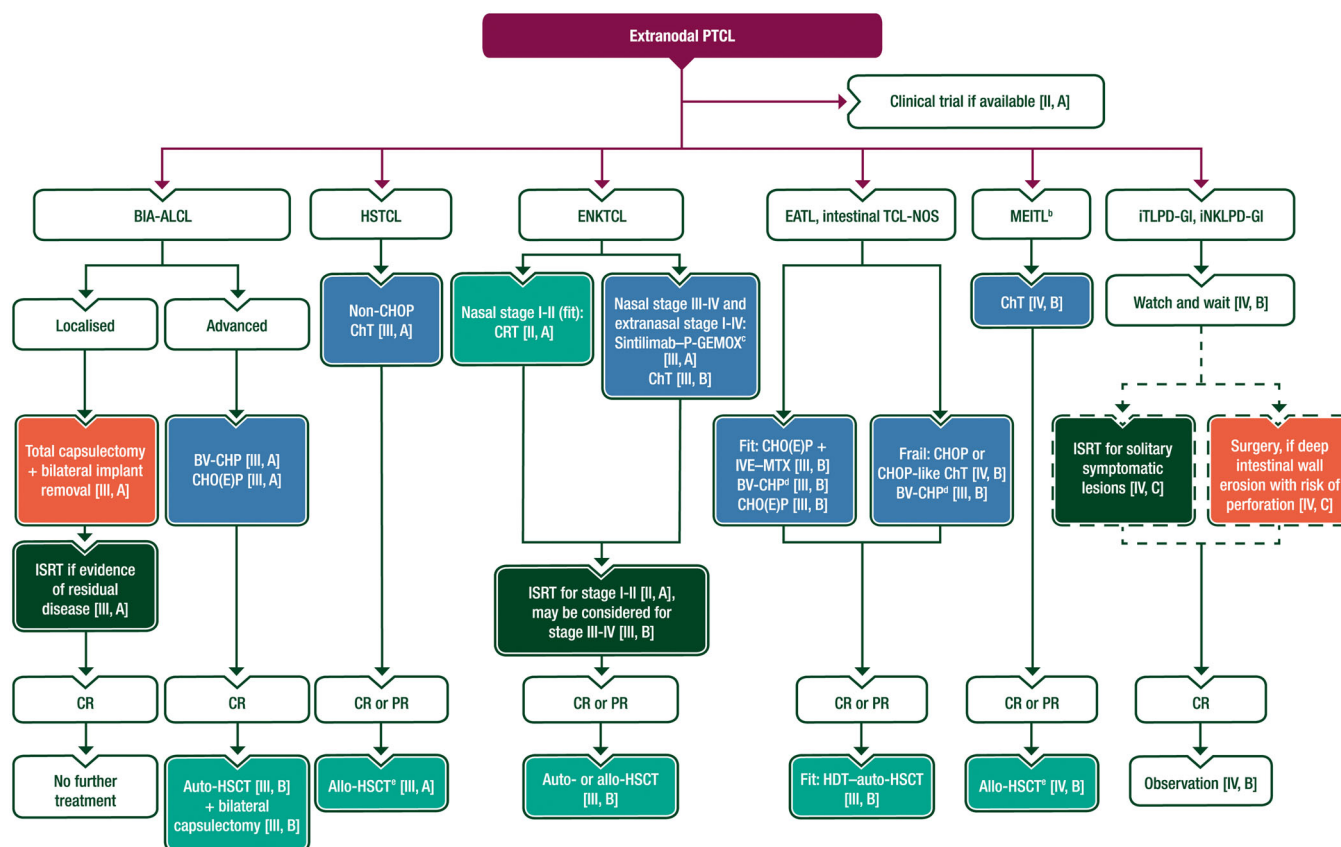


FIGURE 2 Overview of first-line treatment in extranodal PTCL.^a Purple: algorithm title; orange: surgery; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed lines: optional therapy. ALCL, anaplastic large cell lymphoma; allo-HSCT, allogeneic hematopoietic stem-cell transplantation; auto-HSCT, autologous hematopoietic stem-cell transplantation; BIA, breast implant associated; BV-CHP, brentuximab vedotin–cyclophosphamide–doxorubicin–prednisolone; CHO(E)P, cyclophosphamide–doxorubicin–vincristine–(etoposide)–prednisolone; CHOP, cyclophosphamide–doxorubicin–vincristine–prednisolone; ChT, chemotherapy; CR, complete remission; CRT, chemoradiotherapy; EATL, enteropathy-associated T-cell lymphoma; EMA, European Medicines Agency; ENKTCL, extranodal natural killer- or T-cell lymphoma; FDA, Food and Drug Administration; HDT, high-dose chemotherapy; HSTCL, hepatosplenic T-cell lymphoma; iNKLDP-GI, indolent natural killer-cell lymphoproliferative disorders of the gastrointestinal tract; ISRT, involved-site radiotherapy; iTLPD-GI, indolent T-cell lymphoproliferative disorders of the gastrointestinal tract; IVE, ifosfamide–etoposide–epirubicin; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; MTX, methotrexate; NOS, not otherwise specified; P-GEMOX, pegylated L-asparaginase–gemcitabine–oxaliplatin; PR, partial remission; PTCL, peripheral T-cell or natural killer-cell lymphoma; RT, radiotherapy; TCL, T-cell lymphoma. ^aFor subtype-specific treatment algorithms, see Supporting Information: Figures S4–S10. ^bNew entity with insufficient data for clinical recommendation. Small case series suggest poor efficacy of anthracycline-based regimens and biological studies indicate similarities with HSTCL. Consider a strategy similar to HSTCL. ^cNot EMA or FDA approved. ^dFDA approved, not EMA approved. ^eIf chemosensitive (CR or PR), consider early allo-HSCT due to the high risk of early progression.

soft tissue, and skin. Limited-stage disease is uncommon and poorly investigated. In recent retrospective studies of nodal PTCL, including limited-stage ALK-positive and ALK-negative ALCL, good outcomes have been observed after combined modality treatment comprising abbreviated ChT (three to four cycles) consolidated with ISRT.^{34,36,37} A detailed algorithm for the first-line management of ALCL is shown in Supporting Information: Figure S3.

Advanced stage

ECHELON-2 reported significant improvements in PFS and OS with BV-CHP versus CHOP in patients with ALCL, especially those with ALK-positive disease.²³ This benefit was not observed across other PTCL entities. At a median follow-up of 47.6 months, 5-year PFS rates were 51.4% for BV-CHP versus 43.0% for standard CHOP (HR 0.70, 95% confidence interval [CI] 0.53–0.91) and 5-year OS rates were 70.1% versus 61.0%, respectively (HR 0.72, 95% CI

0.53–0.99).³⁸ Entity-specific survival analyses from ECHELON-2 have not yet been reported.

Etoposide

Reports from population-based registries^{20,22} and a retrospective subset analysis of prospective trials¹⁸ demonstrated a survival benefit with CHOEP versus CHOP, particularly in ALK-positive ALCL. Furthermore, a pooled analysis of individual patient data (N = 263) from six clinical studies reported a significant increase in 3-year PFS rate (92% vs. 49%, $p = 0.005$) and OS rate (100% vs. 56%, $p = 0.002$) in patients with ALK-positive ALCL and an IPI ≥ 2 receiving etoposide-containing first-line regimens compared with CHOP.³⁹ Interestingly, the PFS and OS improvements observed with CHOEP were similar to those seen with BV-CHP versus CHOP in ECHELON-2. A single-arm phase II study evaluated the addition of etoposide to BV-CHP (BV-CHEP) in CD30-positive ALCL.⁴⁰ Of 47 patients, 37 achieved a

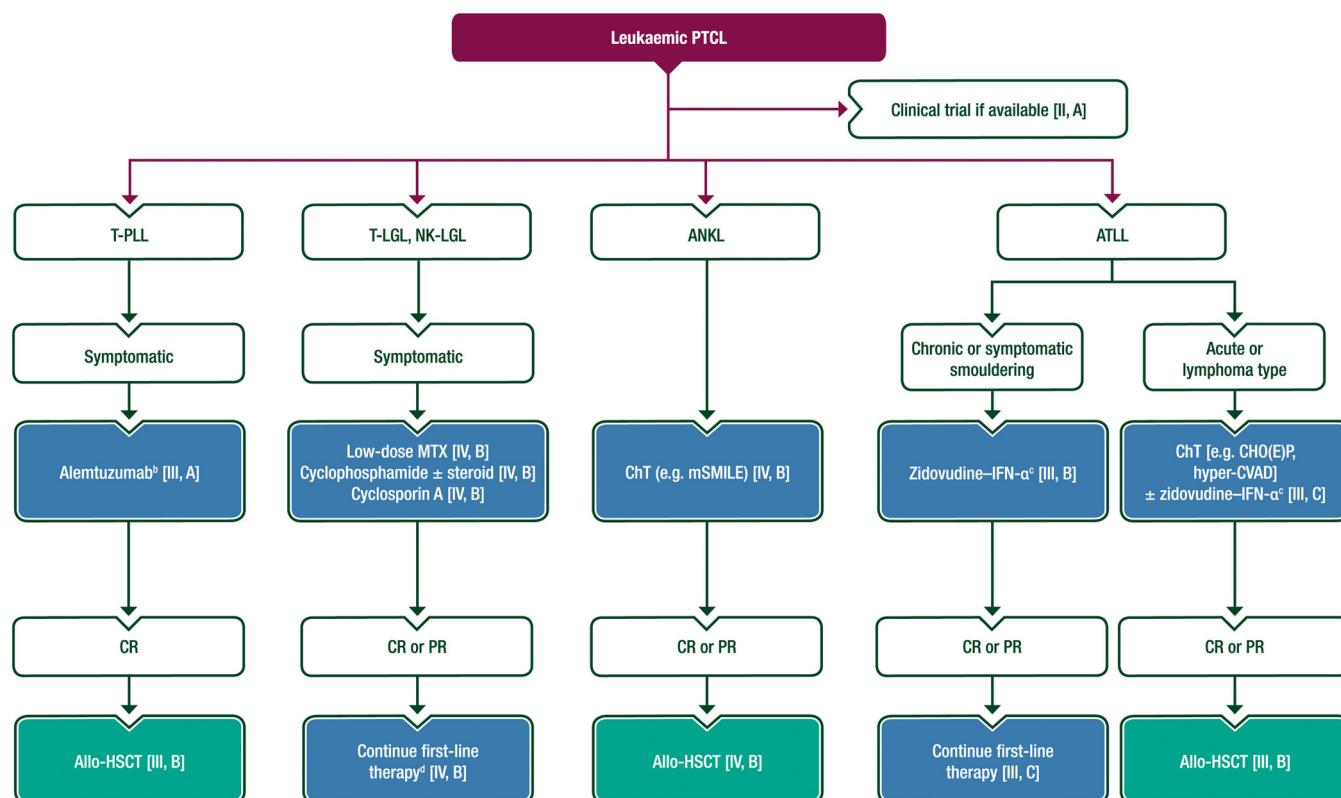


FIGURE 3 Overview of first-line treatment in leukemic PTCL.^a Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects. Allo-HSCT, allogeneic hematopoietic stem-cell transplantation; ANKL, aggressive natural killer-cell leukemia; ATLL, adult T-cell leukemia or lymphoma; CHO(E)P, cyclophosphamide–doxorubicin–vincristine–(etoposide)–prednisolone; ChT, chemotherapy; CR, complete remission; EMA, European Medicines Agency; FDA, Food and Drug Administration; hyper-CVAD, hyperfractionated cyclophosphamide–vincristine–doxorubicin–dexamethasone–methotrexate–cytarabine; IFN- α , interferon- α ; mSMILE, modified dexamethasone–methotrexate–ifosfamide–pegylated L-asparaginase–etoposide; MTX, methotrexate; NK-LGL, natural killer-cell large granular lymphocytic leukemia; PR, partial remission; PTCL, peripheral T-cell or natural killer-cell lymphoma; T-LGL, T-cell large granular lymphocytic leukemia; T-PLL, T-cell prolymphocytic leukemia. ^aFor subtype-specific treatment algorithms, see Supporting Information: Figures S11–S14. ^bNot EMA or FDA approved but available via named-patient access. ^cNot EMA or FDA approved. ^dNo limitation in treatment duration for MTX and cyclosporin A; treatment with cyclophosphamide should be limited to 12 months due to the risk of second malignancy.

CR (79%; 95% CI 64%–89%). BV-CHEP with auto-HSCT yielded better outcomes than BV-CHEP alone.

Role of HSCT

Due to the favorable outcome of low-risk ALK-positive ALCL (IPI < 2 and age < 40 years) after standard CHOP, consolidative auto-HSCT is not recommended in the first remission. In high-risk ALK-positive ALCL (bulky disease, IPI ≥ 2 , age > 40 years, no CR after three ChT cycles) auto-HSCT can be considered on a case-by-case basis. The NLG-T-01 trial reported a 5-year PFS rate of 61% and a 5-year OS rate of 70% in 31 patients with ALK-negative ALCL.¹⁹ In ECHELON-2, a comparative outcome analysis of consolidative HSCT versus no further treatment showed a survival benefit after auto-HSCT in both treatment arms (BV-CHP and CHOP) in patients with ALK-negative ALCL.⁴¹ Interestingly, the survival advantage was more evident in the BV-CHP arm.

BIA-ALCL

Early diagnosis of BIA-ALCL is crucial for optimal outcomes; therefore, raising awareness of potential BIA-ALCL development in

individuals with textured-surface breast implants and associated breast symptoms is important. A multidisciplinary approach is fundamental for staging and optimal treatment, which can limit morbidity and the need for systemic treatment, resulting in better outcomes.⁴² An adapted overview of the TNM (tumor–node–metastasis) staging system for BIA-ALCL, proposed by Clemens et al.⁴³ and modified in Turton et al.⁴² is shown in Supporting Information: Table S5.

Total capsulectomy with removal of the breast implant and excision of any associated mass is the standard treatment for patients with no signs of further disease dissemination (stage IA-IC).⁴³ If enlarged regional lymph nodes are detected on physical examination and/or diagnostic imaging, they should not be assumed to represent lymphoma, as they can be reactively enlarged due to silicone.⁴⁴ A representative biopsy (preferably excision) is preferred. Removal of the contralateral implant, particularly if textured, should be considered since bilateral breast involvement has been reported in ~5% of patients.⁴⁵ In a retrospective study, patients presenting with an isolated seroma with or without an associated tumor mass, but without signs of further disease dissemination, had a good prognosis with a 5-year OS rate of 91% and a 5-year EFS rate of 49%.⁴³ Results were better following complete surgical excision versus partial capsulectomy, systemic ChT, or RT.⁴⁶ Mastectomy or sentinel node

biopsy is not required, since BIA-ALCL is not a disease of the breast parenchyma, except in rare cases of deeply infiltrating disease. Patients with no residual disease on PET-CT after complete surgical excision of stage IA-IC disease can be followed up according to the UK national guidelines without further treatment.⁴² RT may be beneficial for localized residual disease.^{42,43} In patients with more advanced disease (stage IIA-IV), systemic treatment similar to the approach for systemic ALK-negative ALCL should be considered; however, evidence-based data are scarce in this setting and treatment should be defined on a case-by-case basis within a multidisciplinary setting. A detailed algorithm for the first-line management of BIA-ALCL is shown in Supporting Information: Figure S4.

HSTCL

Due to the paucity of prospective data, treatment recommendations for HSTCL are mainly based on results from small, retrospective case series. Aggressive platinum-based regimens (such as ifosfamide-carboplatin-etoposide [ICE]) or ifosfamide-etoposide-cytarabine (IVAC) seem to yield superior outcomes versus CHOP, as reported by a meta-analysis of 166 patients.⁴⁷ Patients treated with CHOP or CHOP-like regimens ($n = 50$) were compared with those who received non-CHOP multiagent ChT-containing platinum, cytarabine, and/or etoposide ($n = 34$). The objective response rate (ORR) was 52% versus 82% ($p = 0.006$) and the median OS was 18 versus 37 months ($p = 0.00014$), respectively. Purine analogs (pentostatin or cladribine), as monotherapy or combined with alemtuzumab, have also been associated with durable responses.⁴⁸ A retrospective study has reported improved outcomes with HSCT consolidation (mostly allo-HSCT due to graft-versus-lymphoma effect) for patients in the first or second remission.⁴⁹ HSCT has also shown efficacy in patients experiencing partial remission (PR) after the first- or second-line therapy. Due to the frequent involvement of the BM in HSTCL, PET-CT-based response assessment should be corroborated by BM biopsy and, if possible, liver biopsy since disseminated, non-focal intrahepatic tumor cell infiltration can be difficult to identify on PET-CT.⁵⁰ A detailed algorithm for the first-line management of HSTCL is shown in Supporting Information: Figure S5.

ENKTCL

Limited stage

Localized ENKTCL most commonly involves the nasal cavity, paranasal sinuses, Waldeyer's ring, and upper aerodigestive tract, but can also affect distant extranasal sites, such as the gastrointestinal (GI) tract, testis, and skin. RT is a central component of first-line treatment for localized disease.⁵¹ Patients with non-bulky stage I disease, or patients with localized disease who are too frail to tolerate ChT, may be treated with RT alone to a dose of ≥ 50 Gy.⁵² The optimal timing for RT is not clearly defined. For fit patients with localized stage I-II disease, concomitant, interposed ("sandwich schedule") or rapidly sequential chemoradiotherapy (CRT), with an early RT dose of ≥ 50 Gy and a platinum- and/or L-asparaginase-containing regimen, have been applied.⁵³ A large retrospective Asian and European study comparing the efficacy of concomitant and sequential CRT in limited-stage ENKTCL reported similar outcomes for both schedules.⁵⁴ ENKTCL is often locally destructive and may infiltrate extensively in the submucosa of the upper aerodigestive tract. A generous ISRT volume is required, covering the entire organ(s) pretherapeutically involved plus adjacent structures with concern for subclinical disease. Advanced

imaging (e.g., PET-CT and MRI for intracranial and facial anatomy) and conformal RT techniques should be applied to guide therapy.⁵⁵ A detailed algorithm for the first-line management of ENKTCL is shown in Supporting Information: Figure S6.

Advanced stage

CHOP or CHOP-like ChT is not used in ENKTCL due to the upregulation of multidrug resistance p-glycoprotein. L-asparaginase is effective as it deprives tumor cells of L-asparagine, an important nutrient that cannot be efficiently synthesized by ENKTCL cells due to innate low L-asparagine synthetase levels.⁵⁶ A prospective trial from the Asia Lymphoma Study Group of 87 patients with ENKTCL (43 de novo and 44 relapsed or refractory [r/r]) evaluating dexamethasone-methotrexate-ifosfamide-pegylated L-asparaginase-etoposide (SMILE) reported an ORR of 81%.⁵⁷ At a median follow-up of 31 months, the 5-year OS rate was 50% and the 4-year disease-free survival rate was 64%. Twenty-four patients received consolidative auto- or allo-HSCT. The cumulative treatment-related mortality rate was 6%–7%. A randomized study of 42 patients comparing dexamethasone-cisplatin-gemcitabine-pegylated L-asparaginase (DDGP) with SMILE showed significantly improved 1-year PFS (86% vs. 38%, $p = 0.006$) and 2-year OS (74% vs. 45%, $p = 0.027$) rates in favor of DDGP, which was also better tolerated.⁵⁸ However, DDGP does not contain blood-brain barrier penetrating agents and may be less suitable for patients at high risk of CNS relapse. The L-asparaginase-methotrexate-dexamethasone (AspMetDex) regimen developed by Jaccard et al. is less intensive than SMILE, has CNS-penetrating capacity and is a good option for older or less fit patients.⁵⁹ Other regimens, such as pegylated L-asparaginase-gemcitabine-oxaliplatin (P-GEMOX),⁶⁰ have shown good efficacy and lower toxicity than SMILE. Very promising efficacy (ORR 100%; CR rate 87.5%) was recently reported in a multicentre phase II study evaluating P-GEMOX combined with the PD-1 inhibitor sintilimab in advanced ENKTCL.⁶¹ At a median follow-up of 16.7 months, median PFS and OS were not reached and the estimated 1-year OS and PFS rates were 100% and 95%, respectively.

Consolidation with HSCT in responding patients

HSCT should be considered for the first-line consolidation in advanced-stage nasal ENKTCL and in distant extranasal disease of all stages, with the arguable exception of truly localized disease. There is no international consensus on which criteria to adopt for selecting auto- or allo-HSCT. A retrospective study based on the European Society for Bone Marrow Transplantation registry analyzed data from 28 patients treated with various first-line regimens and consolidated with auto-HSCT. The 2-year PFS and OS rates were 33% and 40%, respectively.⁶² Regarding allo-HSCT, a retrospective analysis of 82 patients treated with L-asparaginase-containing regimens reported a 3-year OS rate of 35% in white patients and 33% in Asian patients.⁶³ A retrospective analysis of 65 French patients showed, after a median follow-up of 79.9 months, similar 4-year PFS and OS rates for auto- and allo-HSCT (PFS 34% vs. 26%, respectively; OS 52% vs. 53%, respectively).⁶⁴ Response status at HSCT was the major independent prognostic factor for survival (OS HR 4.013, 95% CI 1.137–14.16; PFS HR 5.231, 95% CI 1.625–16.838). Compared with ChT and/or RT alone, consolidative HSCT did not improve outcomes in responding patients, including those treated with L-asparaginase. Despite heterogeneity among studies of allo-HSCT in ENKTCL, a common feature is the low relapse rate beyond 2 years after transplant.⁶³

EATL and intestinal T-cell lymphoma (TCL) NOS

Due to the rarity of EATL and intestinal TCL-NOS, evidence for treatment recommendations is limited, and enrollment in a first-line clinical trial is encouraged. An algorithm for first-line management is shown in Supporting Information: Figure S7. A retrospective study of 26 patients with previously untreated EATL who received one course of CHOP followed by ifosfamide–etoposide–epirubicin (IVE) alternated with intermediate-dose (3 g/m²) methotrexate (MTX) and consolidative high-dose ChT and auto-HSCT (in responding patients) reported median PFS and OS of 3.4 months and 7.1 months, respectively.⁶⁵ The 5-year PFS and OS rates (52% and 60%, respectively) were higher than historical CHOP controls (5-year PFS and OS rates of 20%–22%). Recent interim analyses from an ongoing phase II single-arm trial evaluating BV-CHP and auto-HSCT in responding patients have demonstrated 2-year PFS and OS rates of 63% and 68%, respectively.⁶⁶ Further information on the first-line management of EATL and intestinal TCL-NOS is provided in Supporting Information Section 5.

T-PLL

International T-PLL-specific guidelines were updated in 2019.⁶⁷ An algorithm for the first-line management of T-PLL is shown in Supporting Information: Figure S8. Patients who are symptomatic or have signs of BM insufficiency, and who are HSCT eligible, should be treated with the aim of achieving a CR. The first-line treatment of choice is alemtuzumab.^{68,69} In case of CR, consolidative non-myeloablative allo-HSCT is indicated. Further information on the first-line management of T-PLL is provided in Supporting Information Section 5.

T-LGL and NK-LGL

An algorithm for the first-line management of T-LGL and NK-LGL is shown in Supporting Information: Figure S9. Patients with symptomatic T-LGL or NK-LGL should initially receive monotherapy with drugs used in the treatment of autoimmune diseases. Existing evidence is primarily based on retrospective studies supporting the use of immunosuppressive rather than cytotoxic approaches. The most common first-line drugs are low-dose (weekly) MTX,⁷⁰ cyclophosphamide with or without steroids⁷¹ or cyclosporin A.⁷² The reported ORRs for these approaches in both T-LGL and NK-LGL are in the range of 40%–70% with response durations of 14–36 months.^{70–72} Further information on the first-line management of T-LGL and NK-LGL is provided in Supporting Information Section 5.

Monomorphic epitheliotropic intestinal T-cell lymphoma, type II refractory celiac disease (RCD), indolent T- and NK-cell lymphoproliferative disorders of the GI tract, ANKL, and ATLL

First-line treatment options for monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), type II RCD, indolent T- and NK-cell lymphoproliferative disorders of the GI tract (iTLPD-GI and iNKLPD-GI), ANKL, and ATLL are described in Supporting Information Section 5. Detailed algorithms for the first-line management of these entities are shown in Supporting Information: Figures S10–S14.

Recommendations

- Patients should, whenever possible, be enrolled in a clinical trial (II, A).

PTCL-NOS and TFHL

- CHOP or CHOP-like ChT (e.g., CHOEP) can be recommended as the first-line therapy (II, B).
- In patients with limited-stage, non-bulky disease, and a favorable pre-therapeutic risk profile, an abbreviated course of ChT (e.g., three to four cycles of CHOP or CHOEP) can be considered (IV, B).
- Consolidative ISRT (e.g., 30–40 Gy in 15–20 fractions) can be considered for responding patients with limited-stage disease after CHOP or CHOP-like ChT (IV, B).
- Consolidative auto-HSCT can be considered in responding patients with high-risk limited-stage or advanced disease (III, B).

ALCL, systemic types

- In patients with limited-stage, non-bulky ALK-positive or ALK-negative disease, and a favorable pretherapeutic risk profile (IPI 0–1), an abbreviated course of ChT (e.g., three to four cycles of BV-CHP or CHOEP) can be considered (III, B).
- Six cycles of BV-CHP are recommended for all other ChT-eligible patients (i.e., both ALK negative and ALK positive) (I, A). Alternatively, six cycles of CHO(E)P can be considered (III, B).
- Consolidative ISRT (e.g., 30–40 Gy in 15–20 fractions) can be considered for limited-stage ALCL (IV, B).
- Consolidative auto-HSCT in the first CR can be considered for HSCT-eligible, chemosensitive patients with ALK-negative ALCL (II, B).
- In general, auto-HSCT cannot be recommended for patients with ALK-positive ALCL in the first CR (III, D). It can, however, be considered for patients with high-risk features (IPI ≥ 2, bulky disease) with no CR after three cycles of ChT (III, B).

BIA-ALCL

- A multidisciplinary approach is recommended for diagnostic assessment, staging, and treatment planning (III, A).
- Total capsulectomy with removal of the breast implant and excision of any associated mass is recommended for patients with no signs of further disease dissemination (III, A).
- A representative biopsy (excision preferred) should be obtained if suspicious regional lymph nodes are found (III, A).
- Removal of the contralateral implant is recommended, particularly if textured (III, A).
- Mastectomy cannot be recommended (IV, D).
- ISRT (e.g., 30 Gy in 15 fractions) is recommended following surgery in adapted TNM stage IIA–IIB disease and in stage IA–IC disease if there is evidence of residual disease (III, A).
- Six cycles of BV-CHP, CHOP, or CHOEP is recommended for patients with residual disease following ISRT and those with advanced disease (stages III–IV) (III, A).
- Auto-HSCT can be considered in responding patients following ChT (III, B).
- Bilateral capsulectomy can be considered in responding patients with advanced disease following ChT (III, B).

HSTCL

- In the absence of clinical trials, ChT that is more aggressive than CHOP is recommended for fit and HSCT-eligible patients (III, A).
- ICE is suggested as the preferred regimen for first-line therapy (IV, B). Other options include IVAC, dexamethasone–high-dose cytarabine–

cisplatin (DHAP), dexamethasone–cytarabine–oxaliplatin (DHAX), and CHOEP (IV, C).

- ChT options for frail and/or HSCT-ineligible patients include dose-reduced ICE and gemcitabine–oxaliplatin (GEMOX) (IV, C).
- Due to the frequent involvement of the BM in HSTCL, response assessment via PET–CT should be corroborated by BM biopsy and, if possible, liver biopsy, since diffuse intrahepatic tumor cell infiltration can be difficult to identify on PET–CT (III, A).
- If possible, BM and peripheral blood specimens should be analyzed by flow cytometry for assessment of surface antigens on tumor cells that are not reliably identifiable by routine IHC (e.g., CD52) (III, B).
- Eligible responding (CR or PR) patients should undergo consolidative HSCT, preferably allo-HSCT (III, A). Auto-HSCT is recommended for patients who are ineligible for allo-HSCT (III, A).

ENKTCL

- EBV DNA in peripheral blood should be monitored by quantitative PCR at baseline and during therapy as a biomarker of response, in addition to imaging-based response assessment (II, A).
- Fit patients with limited-stage disease should receive ISRT (≥ 50 Gy) with concurrent, interposed, or sequential anthracycline-free, L-asparaginase-containing ChT (e.g., DDGP or modified SMILE [mSMILE] for HSCT-eligible and AspMetDex or P-GEMOX for HSCT-ineligible patients) (II, A).
- A multiagent, anthracycline-free, L-asparaginase-containing regimen can be recommended for patients with stages III and IV nasal disease or stages I–IV extranasal disease (e.g., DDGP or mSMILE for HSCT-eligible and AspMetDex or P-GEMOX for HSCT-ineligible patients) (III, B). The addition of ISRT can be decided on a case-by-case basis (III, B).
- First-line treatment with anti-PD-1 antibodies such as sintilimab (not European Medicines Agency [EMA] or Food and Drug Administration [FDA] approved) in combination with L-asparaginase-containing regimens (e.g., P-GEMOX) should also be considered in patients with stages III and IV nasal disease or stages I–IV extranasal disease (III, A).
- If available, crisantaspase (*Erwinia chrysanthemi*-derived L-asparaginase) is recommended for patients who have developed hypersensitivity or inactivating antibodies to *Escherichia coli*-derived L-asparaginase (III, A; not EMA or FDA approved in ENKTCL).
- In HSCT-eligible responding high-risk patients, consolidative auto- or allo-HSCT can be considered (III, B). The choice of HSCT should be made on a case-by-case basis considering factors such as pretherapeutic risk profile, response to first-line therapy, performance status (PS), and donor availability (III, B).

EATL and intestinal TCL-NOS

- In fit and HSCT-eligible patients, one cycle of CHOP or CHOEP, followed by three cycles of IVE alternated with intermediate-dose MTX can be recommended (III, B). Alternative regimens are six cycles of BV-CHP (FDA approved, not EMA approved), CHOP, or CHOEP (III, B).
- Consolidative high-dose ChT–auto-HSCT can be considered for HSCT-eligible responding patients (III, B).
- Six cycles of CHOP or CHOP-like ChT (IV, B) or six cycles of BV-CHP (III, B; FDA approved, not EMA approved) can be recommended for frail or otherwise HSCT-ineligible patients.

T-PLL

- A watch-and-wait approach can be recommended for asymptomatic T-PLL (III, B).
- Alemtuzumab (given intravenously with a dose escalation of 3, 10, and 30 mg in the first week followed by 30 mg three times per week over a total of 10–12 weeks) is recommended for newly diagnosed symptomatic T-PLL (III, A; not EMA or FDA approved but available via named-patient access).
- Assessment of CD52 status by flow cytometry can be recommended before, during, and after treatment (III, B).
- During alemtuzumab therapy, antimicrobial prophylaxis against herpes zoster and *Pneumocystis jirovecii* is recommended, as well as quantitative cytomegalovirus DNA monitoring (III, A).
- Consolidative non-myeloablative allo-HSCT can be recommended in eligible patients achieving CR who have a donor (III, B); otherwise, auto-HSCT can be considered on a case-by-case basis (IV, C).

T-LGL and NK-LGL

- Asymptomatic patients without severe cytopenias or substantial splenomegaly can be managed initially by observation only (IV, B).
- Symptomatic patients (e.g., transfusion-requiring anemia and/or thrombocytopenia, severe neutropenia [neutrophils $<0.5 \times 10^9/L$] and/or symptomatic splenomegaly) can begin immunosuppressive first-line treatment with low-dose weekly MTX (preferred in patients with associated autoimmune disease), cyclophosphamide (with or without a steroid) or cyclosporin A (the last two preferred in patients with severe cytopenias) (IV, B).
- The efficacy of first-line treatment can be evaluated after 3–4 months, and the same treatment can continue if response (CR or PR) and feasibility are satisfactory (IV, B).

MEITL

- Non-CHOP multiagent ChT can be recommended (preferred) (IV, B).
 - Options for HSCT-eligible patients include ICE (preferred), IVAC, DHAP, DHAX, and CHOEP (IV, B).
 - Options for HSCT-ineligible patients include dose-reduced ICE, gemcitabine–dexamethasone–cisplatin (GDP), and GEMOX (V, B).
- Allo-HSCT consolidation can be considered in chemosensitive (CR or PR) HSCT-eligible patients with a suitable donor (IV, B).

Type II RCD

- If aberrant, clonal intraepithelial lymphocytes are found, small bowel imaging with capsule endoscopy and a PET–CT scan (possibly supplemented by magnetic resonance enterography) should be carried out to exclude EATL and ulcerative jejunoileitis (III, A).
- Tissue biopsies should be examined by an experienced hematopathologist to identify lesions suggestive of EATL (including CD30 expression) (III, A).
- If EATL is diagnosed, specific management for this entity should be initiated. If not, checks for EATL, including small bowel imaging in case of new symptoms or signs concerning for EATL, at 6–12-month intervals can be considered (IV, B).

iTLPD-GI and iNKLPD-GI

- Aggressive approaches based on conventional combination ChT should only be used in case of verified dissemination and/or histological transformation (IV, B).
- An observational approach can be recommended, focusing primarily on ruling out disease progression and dissemination (IV, B). Individual lesions may be endoscopically verified for risk of intestinal wall perforation (e.g., presence of deep erosions) (IV, C).
- ISRT may be considered in case of solitary symptomatic lesions (IV, C).
- Limited surgical resection may be considered in case of deep intestinal wall erosion (e.g., superficial mucosal erosion deepened by subsequent local infection or inflammation) with a high perforation risk (IV, C).

ANKL

- In fit, HSCT-eligible patients, an intensive L-asparaginase-containing ChT first-line regimen (e.g., mSMILE) can be recommended (IV, B), with the aim of consolidating a primary response with allo-HSCT (IV, B).
- In patients who are frail and/or HSCT ineligible, a non-intensive L-asparaginase-containing ChT regimen (e.g., AspMetDex) can be considered (IV, B).

ATLL

- Testing for HTLV-1 can be recommended in first-degree relatives and partners of patients with ATLL (II, B).
- Antimicrobial prophylaxis for opportunistic infections can be recommended for all patients (II, B). In case of positive *Strongyloides stercoralis* serology, treatment can be initiated even if the patient is asymptomatic (III, B).
- Asymptomatic smoldering ATLL can be managed with active monitoring without immediate therapeutic intervention (III, B).
- Zidovudine–interferon- α (IFN- α) can be recommended for patients with symptomatic smoldering (skin or lung lesions, opportunistic infections), primary cutaneous with tumoural lesions or chronic ATLL (III, B; not EMA or FDA approved), along with skin-directed therapy in case of skin lesions (III, B).
- CNS prophylaxis can be recommended for all patients with acute or lymphoma-type ATLL (III, B).
- High-dose zidovudine–IFN- α can be recommended as first-line therapy for patients with acute, non-bulky, non-lymphomatous ATLL whenever feasible, particularly for those who are unsuitable for intensive ChT or allo-HSCT (III, B; not EMA or FDA approved).
- Patients with acute or lymphoma-type ATLL with bulky lesions may receive intensive combination ChT (e.g., CHOP, CHOEP or hyperfractionated cyclophosphamide–vincristine–doxorubicin–dexamethasone–MTX–cytarabine [hyper-CVAD]) with or without concurrent or sequential zidovudine–IFN- α (if tolerated) (III, C; not EMA or FDA approved).
- Chemosensitive patients can proceed to allo-HSCT (III, B). An antiretroviral agent can be added to the conditioning regimen to prevent HTLV-1 neo-infection of donor cells (III, B).
- Responding patients who are ineligible for allo-HSCT may receive maintenance therapy with zidovudine–IFN- α with or without arsenic trioxide (III, C; not EMA or FDA approved). If zidovudine–IFN- α is poorly tolerated or there is no longer a response, oral low-dose etoposide may be considered as monotherapy or as part of a regimen (III, C).

TREATMENT OF R/R DISEASE

Patients with r/r PTCL have a poor prognosis, with a study reporting median PFS and OS of 3.1 months and 5.5 months, respectively.⁷³ Algorithms for the management of r/r PTCL are shown in Figure 4 (r/r nodal PTCL), Figure 5 (r/r extranodal PTCL), and Figure 6 (r/r leukemic PTCL).

r/r nodal and extranodal PTCL, except ALK-positive ALCL, ENKTCL, iTLPD-GI, and iNKLPD-GI

Allo-HSCT is the best curative option for HSCT-eligible, chemosensitive patients, if not already applied. The poor prognosis justifies enrollment in a clinical trial whenever possible; otherwise, ChT used to treat r/r DLBCL (e.g., ICE, DHAP, and GDP) is widely used, although efficacy data are limited. BV monotherapy has shown efficacy in ALK-negative ALCL.^{74,75} Single-agent romidepsin,⁷⁶ belinostat⁷⁷ and pralatrexate⁷⁸ have been conditionally approved by the FDA but not by the EMA. The phosphoinositide 3-kinase (PI3K) δ and PI3K γ inhibitor duvelisib have demonstrated efficacy⁷⁹ but are not approved for use in PTCL. Bendamustine has demonstrated an ORR of 50%, although response duration is usually short.⁸⁰ Cyclosporin A, lenalidomide, and 5-aza have shown efficacy in r/r AITL.^{81–83} Oral 5-aza has also been investigated in a phase III trial of r/r TFHL, comparing it with investigator's choice of gemcitabine, bendamustine, or romidepsin.⁸⁴ Although the trial did not meet its primary endpoint (superior PFS in the experimental arm), 5-aza was associated with prolonged OS and a favorable safety profile, suggesting it could be useful in some patients with TFHL. Notably, romidepsin, bendamustine, cyclosporin A, lenalidomide, 5-aza, and gemcitabine given as monotherapy have achieved ORRs <40%, with rare sustained responses.

HSCT

Data supporting auto-HSCT consolidation in chemosensitive r/r PTCL are limited and based on retrospective series, with a 3-year OS rate of ~50%. Patients may experience sustained response and prolonged survival after allo-HSCT,⁸⁵ with retrospective series reporting a 5-year OS rate of ~50%. The type of conditioning regimen does not seem to affect failure rate, PFS or OS, suggesting that less-toxic, non-myeloablative conditioning should be favored.⁸⁶ Recent data suggest that transplantation using a haploidentical donor provides similar outcomes to a matched related donor.⁸⁷

r/r ALK-positive ALCL

Patients with r/r ALK-positive ALCL benefit from BV monotherapy (ORR 86%, CR rate 57%)⁸⁸; however, most patients receive BV-CHP in first line. Limited data suggest that patients achieving a sustained response after first-line BV-containing treatment could benefit from BV retreatment⁸⁹; however, the relevance of BV retreatment as monotherapy or in combination with ChT in the r/r setting is unclear. For patients who are refractory to BV, first-generation (e.g., crizotinib) and second-generation (e.g., alectinib, brigatinib, ceritinib) ALK inhibitors have been associated with CR rates of 25%–80% and a 1-year PFS rate of 60%.^{90–92} Responding patients should undergo consolidation; auto-HSCT was associated with poor outcomes in a cohort of patients aged ≤ 21 years, supporting the use of allo-HSCT.⁹³

r/r ENKTCL

The anti-PD-1 antibodies pembrolizumab and nivolumab have induced responses in r/r ENKTCL following L-asparaginase-

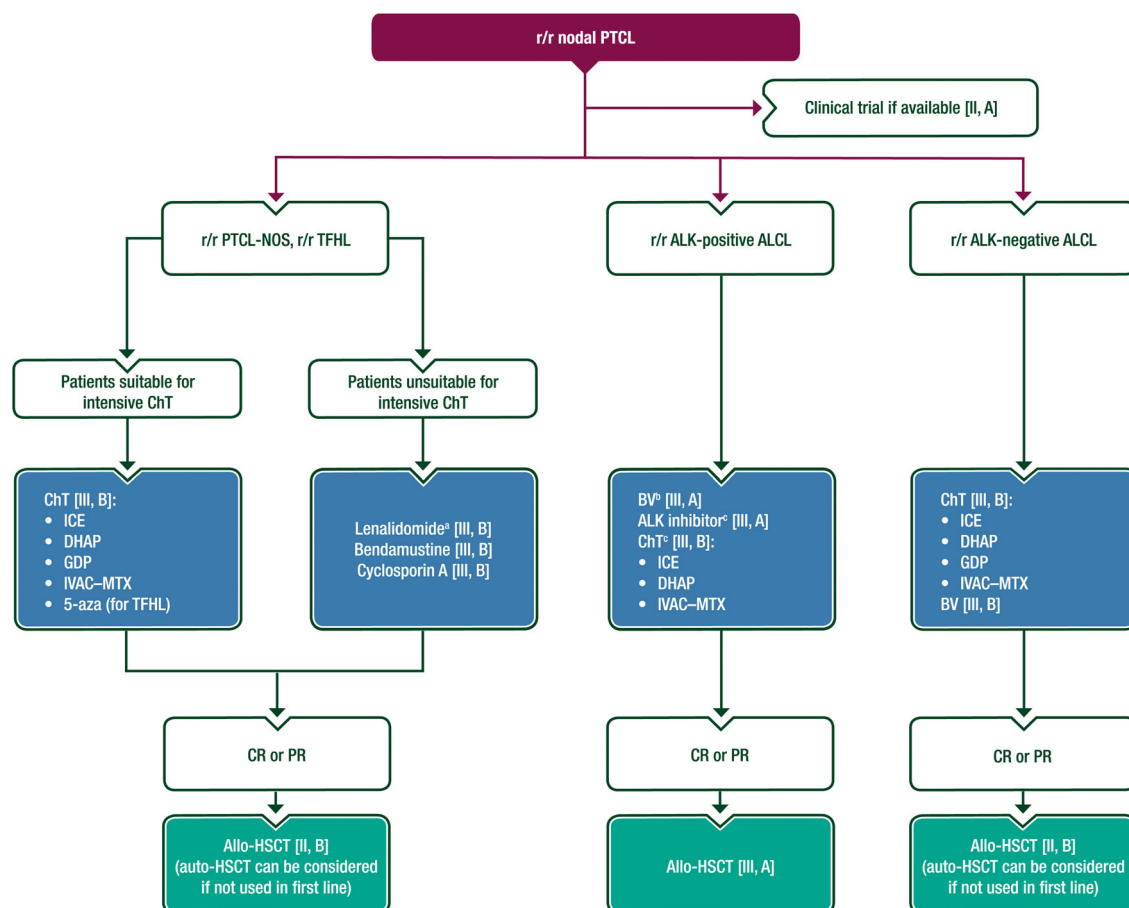


FIGURE 4 Treatment of r/r nodal PTCL. Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects. 5-aza, 5-azacitidine; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; allo-HSCT, allogeneic hematopoietic stem-cell transplantation; auto-HSCT, autologous hematopoietic stem-cell transplantation; BV, brentuximab vedotin; ChT, chemotherapy; CR, complete remission; DHAP, dexamethasone-high-dose cytarabine-cisplatin; EMA, European Medicines Agency; FDA, Food and Drug Administration; GDP, gemcitabine-dexamethasone-cisplatin; ICE, ifosfamide-carboplatin-etoposide; IVAC, ifosfamide-etoposide-cytarabine; MTX, methotrexate; NOS, not otherwise specified; PR, partial remission; PTCL, peripheral T-cell or natural killer-cell lymphoma; r/r, relapsed or refractory; TFHL, follicular helper T-cell derived lymphoma. ^aNot EMA or FDA approved. ^bPatients who did not receive first-line BV or those with late relapse after an initial response. ^cPatients refractory to BV.

based regimens.^{94,95} BV efficacy has been demonstrated only in anecdotal case reports of CD30-positive r/r ENKTCL.⁹⁶ For HSCT-eligible patients responding to salvage therapy, HSCT (preferably allo-HSCT) is an option based on small case series and case reports.⁶⁴

r/r T-PLL

r/r T-PLL is an extremely treatment-refractory condition with limited therapeutic options that can induce responses to allow consolidative allo-HSCT in HSCT-eligible patients. Inclusion in a clinical trial should always be considered. A new course of alemtuzumab, preferably in combination with a purine analog (e.g., pentostatin), should be considered at relapse after a treatment-free period of ≥ 6 months in patients who still have CD52-positive tumor cells.⁶⁷ A phase II study of 13 patients with r/r T-PLL who received alemtuzumab-pentostatin reported an ORR of 69%, median OS of 10.2 months, and median PFS of 7.8 months.⁴⁸

r/r T-LGL and NK-LGL

Alemtuzumab was investigated prospectively in 25 patients with T-LGL (23 with r/r T-LGL), of which six were diagnosed with T-LGL after allo-HSCT transplant or co-existing with a myelodysplastic syndrome.⁹⁷ The 19 patients with “classical” T-LGL had a 3-month ORR of 74% and a 12-month ORR of 68%. *STAT3* mutational status had no prognostic impact. Purine analogs (pentostatin, cladribine, fludarabine) and splenectomy have also shown some activity in r/r T-LGL and NK-LGL in small case series or individual case reports. Ruxolitinib has demonstrated preliminary efficacy in r/r T-LGL and across other PTCL subtypes.^{98,99}

r/r iTLPD-GI, iNKLPD-GI, ANKL, and ATLL

Treatment options for r/r iTLPD-GI, iNKLPD-GI, ANKL, and ATLL are described in Supporting Information Section 6.

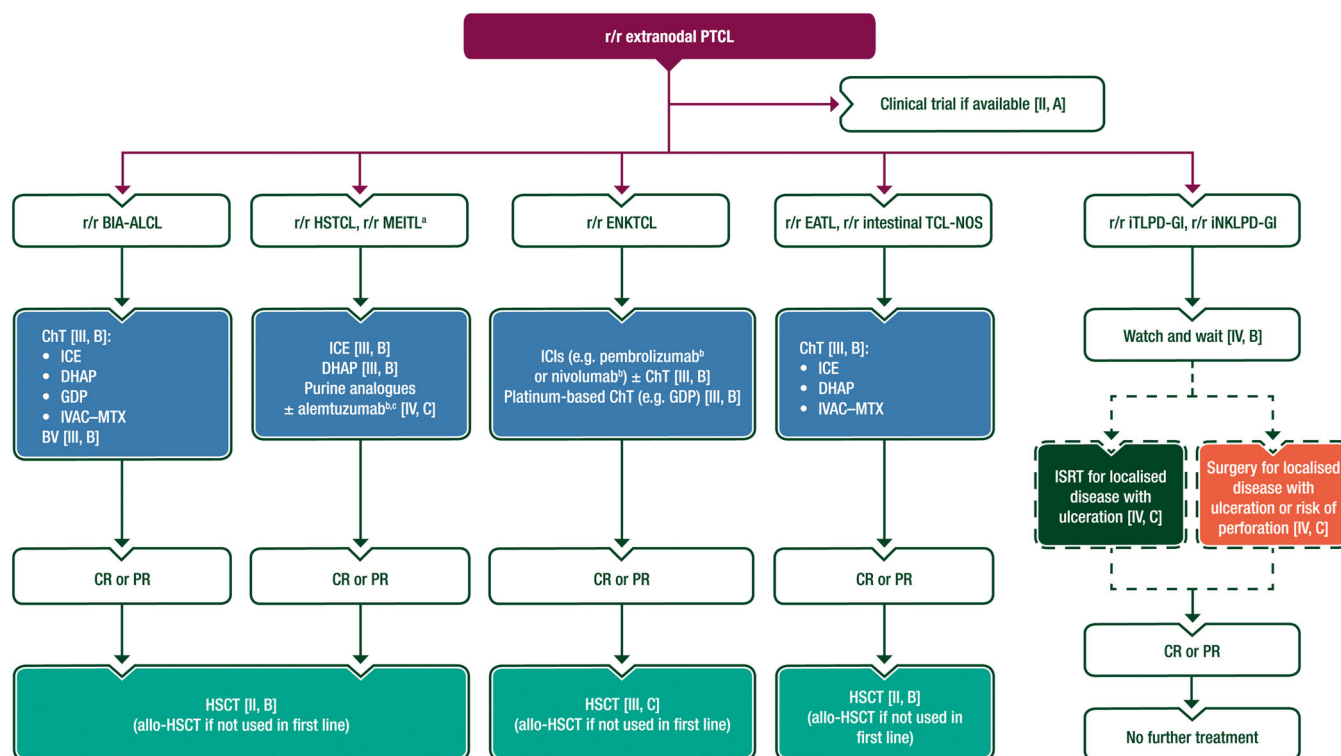


FIGURE 5 Treatment of r/r extranodal PTCL. Purple: algorithm title; orange: surgery; dark green: RT; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed lines: optional therapy. ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; allo-HSCT, allogeneic hematopoietic stem-cell transplantation; BIA, breast implant associated; BM, bone marrow; BV, brentuximab vedotin; CD, cluster of differentiation; ChT, chemotherapy; CR, complete remission; DHAP, dexamethasone-high-dose cytarabine-cisplatin; EATL, enteropathy-associated T-cell lymphoma; EMA, European Medicines Agency; ENKTCL, extranodal natural killer- or T-cell lymphoma; FDA, Food and Drug Administration; GDP, gemcitabine-dexamethasone-cisplatin; HSCT, hematopoietic stem-cell transplantation; HSTCL, hepatosplenic T-cell lymphoma; ICE, ifosfamide-carboplatin-etoposide; ICI, immune checkpoint inhibitor; iNKLPD-GI, indolent natural killer-cell lymphoproliferative disorders of the gastrointestinal tract; ISRT, involved-site radiotherapy; iTLPD-GI, indolent T-cell lymphoproliferative disorders of the gastrointestinal tract; IVAC, ifosfamide-etoposide-cytarabine; MEITL, monomorphic epithelioid intestinal T-cell lymphoma; MTX, methotrexate; NOS, not otherwise specified; PR, partial remission; PTCL, peripheral T-cell or natural killer-cell lymphoma; r/r, relapsed or refractory; RT, radiotherapy; TCL, T-cell lymphoma. ^aNo specific recommendations available. Due to shared biological features, consider treating as r/r HSTCL. ^bNot EMA or FDA approved. ^cConsider alemtuzumab if CD52-positive tumor cells demonstrated by flow cytometry (e.g., BM or peripheral blood sample).

Recommendations

- The poor prognosis of r/r PTCL justifies patient inclusion in a clinical trial whenever possible (II, A).

r/r nodal and extranodal PTCL, except ALK-positive ALCL, ENKTCL, iTLPD-GI, and iNKLPD-GI

- If a clinical trial is not available, platinum-based regimens that are non-cross resistant to the first-line anthracycline-based ChT can be considered (III, B).
 - Options for r/r PTCL-NOS and TFHL include ICE, DHAP, GDP, IVAC-MTX, and 5-aza (for TFHL only) (III, B). Options for patients who are not fit enough for intensive ChT include lenalidomide (not EMA or FDA approved), bendamustine, and cyclosporin A (III, B).
 - Options for r/r ALK-negative ALCL and BIA-ALCL include ICE, DHAP, GDP, IVAC-MTX (III, B). BV monotherapy is also an option (III, B).
 - Options for r/r HSTCL and MEITL include ICE and DHAP (III, B). A purine analog with or without alemtuzumab is also an option if

CD52-positive tumor cells are demonstrated by flow cytometry (e.g., BM or peripheral blood sample) (IV, C; not EMA or FDA approved).

- Options for r/r EATL and intestinal TCL-NOS include ICE, DHAP, and IVAC-MTX (III, B).
- For HSCT-eligible patients responding to salvage therapy, HSCT (preferably allo-HSCT if not used in first line) can be considered (II, B).

r/r ALK-positive ALCL

- BV is recommended in patients who did not receive first-line BV or those with late relapse after an initial response (III, A).
- For patients refractory to BV, ALK inhibitors such as crizotinib (EMA and FDA approved in children and young adults), alectinib (not EMA or FDA approved), brigatinib (not EMA or FDA approved), or ceritinib (not EMA or FDA approved) should be considered (III, A). ChT (e.g., ICE, DHAP, or IVAC-MTX) is also an option (III, B).
- Consolidative allo-HSCT should be considered, based on response to salvage therapy, current remission quality, comorbid conditions, and predicted tolerability (III, A).

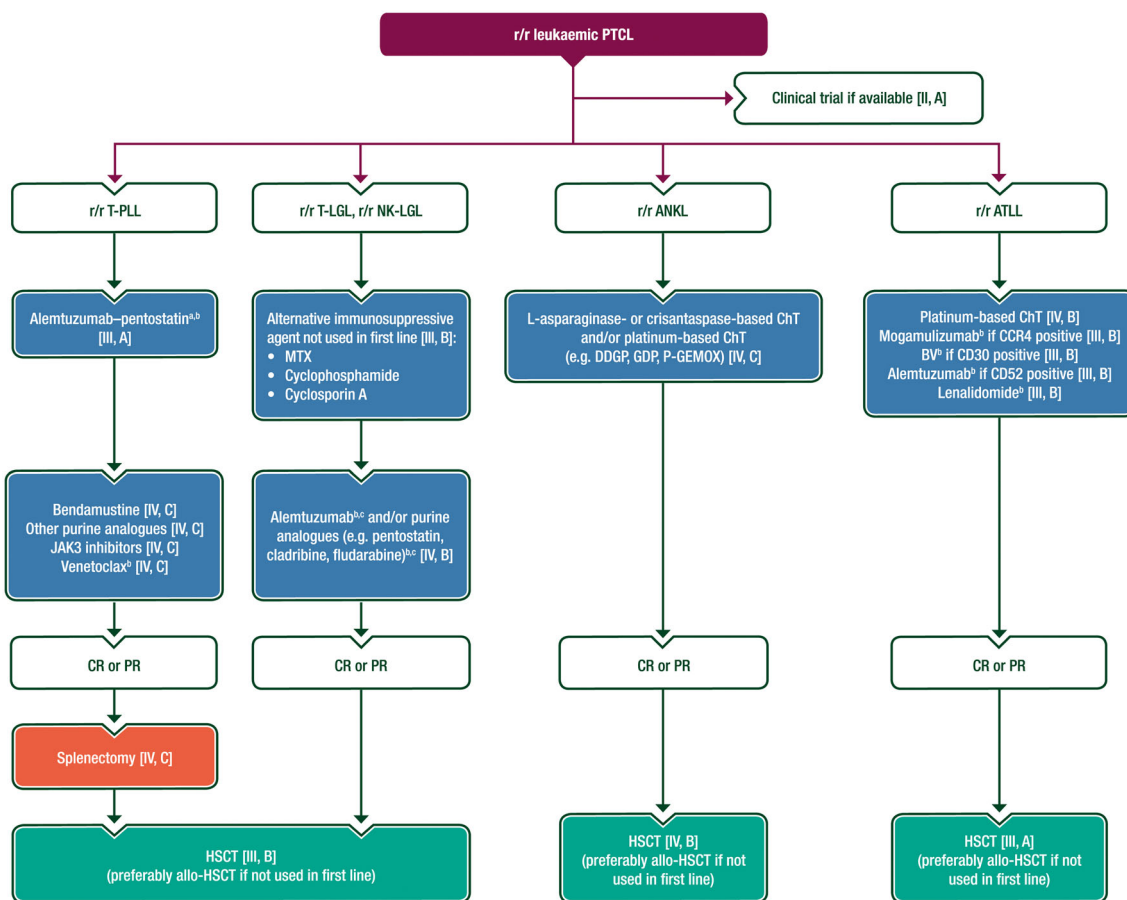


FIGURE 6 Treatment of r/r leukemic PTCL. Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects. Allo-HSCT, allogeneic hematopoietic stem-cell transplantation; ANKL, aggressive natural killer-cell leukemia; ATLL, adult T-cell leukemia or lymphoma; BV, brentuximab vedotin; CCR4, C-C chemokine receptor type 4; CD, cluster of differentiation; ChT, chemotherapy; CR, complete remission; DDGP, dexamethasone-cisplatin-gemcitabine-pegylated L-asparaginase; EMA, European Medicines Agency; FDA, Food and Drug Administration; GDP, gemcitabine-dexamethasone-cisplatin; HSCT, hematopoietic stem-cell transplantation; JAK3, Janus kinase 3; MTX, methotrexate; NK-LGL, natural killer-cell large granular lymphocytic leukemia; P-GEMOX, pegylated L-asparaginase-gemcitabine-oxaliplatin; PR, partial remission; PTCL, peripheral T-cell or natural killer-cell lymphoma; r/r, relapsed or refractory; T-LGL, T-cell large granular lymphocytic leukemia; T-PLL, T-cell prolymphocytic leukemia. ^aAfter a treatment-free period of ≥ 6 months in patients who still have CD52-positive tumor cells. ^bNot EMA or FDA approved. ^cIn patients who do not respond to MTX, cyclophosphamide, or cyclosporin A.

r/r ENKTCL

- If available, an anti-PD-1 antibody such as pembrolizumab (not EMA or FDA approved) or nivolumab (not EMA or FDA approved) can be considered as monotherapy or in combination with gemcitabine and/or L-asparaginase or crisantaspase (III, B).
- As an alternative, platinum-based regimens (e.g., GDP) can be considered (III, B).
- For HSCT-eligible patients responding to salvage therapy, HSCT (preferably allo-HSCT if not used in first line) may be considered (III, C).

r/r T-PLL

- Alemtuzumab-pentostatin is recommended after a treatment-free period of ≥ 6 months in patients who still have CD52-positive tumor cells (III, A; not EMA or FDA approved). Bendamustine, other

purine analogs, JAK3 inhibitors, and venetoclax (not EMA or FDA approved) are options following alemtuzumab-pentostatin (IV, C).

- Splenectomy may be considered in responding patients (IV, C).
- Consolidative HSCT (preferably allo-HSCT if not used in first line) can be recommended for HSCT-eligible responding patients (III, B).

r/r T-LGL and NK-LGL

- An alternative immunosuppressive agent from the list of those suggested for first-line treatment (MTX, cyclophosphamide, cyclosporin A) can be considered (III, B).
- Alemtuzumab (not EMA or FDA approved) and/or purine analogs (not EMA or FDA approved; e.g., pentostatin, cladribine, fludarabine) can be considered in patients who do not respond to MTX, cyclophosphamide, or cyclosporin A (IV, B).
- Consolidative HSCT (preferably allo-HSCT if not used in first line) can be recommended for HSCT-eligible responding patients (III, B).

r/r iTLPD-GI and iNKLPD-GI

- Watch and wait can be recommended (IV, B), with ISRT considered for localized disease with ulceration (IV, C) and surgery as an option for localized disease with ulceration or risk of perforation (IV, C).

r/r ANKL

- If a clinical trial is not available and patient PS allows, an alternative L-asparaginase- or crisantaspase- and/or platinum-based regimen (e.g., DDGP, GDP, P-GEMOX) may be considered (IV, C).
- Allo-HSCT (if not used in first line) can be considered in HSCT-eligible patients who are responding to salvage therapy (IV, B).

r/r ATLL

- A second-line platinum-based regimen can be considered (IV, B).
- Monotherapy with mogamulizumab (if CCR4-positive; not EMA or FDA approved), BV (if CD30-positive; not EMA or FDA approved), alemtuzumab (if CD52-positive; not EMA or FDA approved), or lenalidomide (not EMA or FDA approved) can be considered (III, B).
- Allo-HSCT (if not used in first line) should be considered in HSCT-eligible responding patients (III, A).
- In case of planned allo-HSCT, mogamulizumab should not be administered within 50 days before allo-HSCT (III, A).

RESPONSE EVALUATION AND FOLLOW-UP

Response evaluation and follow-up in patients with PTCL are described in Supporting Information Section 7.

Recommendations

- An interim evaluation can be carried out to assess chemosensitivity (II, B).
- Diagnostic imaging (preferably PET-CT) can be repeated at EOT along with a BM biopsy, if initially involved (II, B).
- Interim PET response has outcome-predictive value in nodal PTCLs, except for ALK-positive ALCL (II, B).
- Follow-up may include history and physical examination every 3 months for 1 year and every 6 months for 2 further years (non-auto-HSCT consolidated patients) or 4 further years (auto-HSCT consolidated patients) (IV, C).
- Routine surveillance with PET-CT or diagnostic CT cannot be recommended for patients with CR (III, D).
- EBV DNA monitoring is recommended for patients with ENKTCL (II, A) and is optional for patients with nodal PTCL and circulating EBV DNA at diagnosis (IV, C).
- Follow-up can be discontinued after 3 years in non-transplanted asymptomatic patients (III, B) and after 5 years in asymptomatic patients who have received auto-HSCT (III, B), if the patient is considered to be in ongoing CR. In patients who have received allo-HSCT, the general guidelines for allo-HSCT should be applied (III, A).

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (<http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>). The relevant literature

has been selected by the expert authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supporting Information: Table S6. Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: <https://www.esmo.org/guidelines/guidelines-by-topic/haematological-malignancies/peripheral-t-cell-lymphomas>.

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AUTHOR CONTRIBUTIONS

All authors conceptualized, performed the literature search, and reviewed and edited the manuscript. Francesco d'Amore and Massimo Federico performed the literature review and development of clinical recommendations. Francesco d'Amore and Laurence de Leval visualized the work. Francesco d'Amore, Laurence de Leval, Massimo Federico, François Lemonnier, Olivier Hermine, Fredrik Ellin, and Joost S. P. Vermaat wrote the original draft. The following authors contributed to section-specific contributions: epidemiology, staging and risk assessment, follow-up—Fredrik Ellin, Massimo Federico, and Francesco d'Amore; diagnosis and pathology—Laurence de Leval and Joost S. P. Vermaat; primary treatment—Francesco d'Amore, François Lemonnier, Olivier Hermine, Massimo Federico, Won Seog Kim, Gerald Wulf, and Fredrik Ellin; treatment of relapsed/refractory disease—Francesco d'Amore, François Lemonnier, Olivier Hermine, Massimo Federico, Won Seog Kim, Gerald Wulf, and Fredrik Ellin.

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F. d. A. reports institutional fees for an advisory role from Frost; institutional fees as local principal investigator (PI) from Genmab; institutional fees for the implementation of a clinical trial as co-ordinating PI from Servier; non-remunerated membership of the Scientific Committee for the European School of Haematology and the Clinical Advisory Committee for the WHO (T-cell lymphoma working group); and non-remunerated roles as project lead for the European Union's HARMONY Alliance (contact person of associated member institution Aarhus University Hospital), lead author of ESMO-EHA CPG for T-cell lymphomas, Chairman of the Nordic Lymphoma Group (NLG) T-cell lymphoma working group and PI for the RESILIENCE trial at Aarhus University Hospital.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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