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Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. d'Amore[1], P. Gaulard[2], L. Trümper[3], P. Corradini[4], W.-S. Kim[5], L. Specht[6], M. Bjerregaard Pedersen[1] & M. Ladetto[7], on behalf of the ESMO Guidelines Committee*

[1]*Department of Hematology, Aarhus University Hospital, Aarhus, Denmark;* [2]*Department of Pathology, Hôpital Henri Mondor, Créteil, France;* [3]*Department of Hematology and Oncology, Georg August University, Göttingen, Germany;* [4]*Department of Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, University of Milan, Milan, Italy;* [5]*Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Seoul, Korea;* [6]*Department of Oncology and Hematology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;* [7]*Divisione di Ematologia, Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo, Alessandria, Italy*

introduction

The present guidelines cover the systemic subtypes of primary nodal and primary extranodal peripheral T-cell lymphomas (PTCLs). ESMO guidelines for primary cutaneous T-cell lymphomas are published separately [1]. Primary leukaemic PTCL subtypes (i.e. T-cell prolymphocytic leukaemia, T-cell large granular lymphocytic leukaemia, adult T-cell leukaemia/lymphoma and aggressive NK-cell leukaemia) are not covered by the present guidelines. Primary nodal PTCLs include PTCL-not otherwise specified (PTCL-NOS), anaplastic large-cell lymphoma (ALCL), both fusion protein ALCL anaplastic lymphoma kinase positive (ALCL ALK+) and ALCL anaplastic lymphoma kinase negative (ALCL ALK−), and angioimmunoblastic T-cell lymphoma (AITL). The primary extranodal PTCL subtypes covered by the present guidelines comprise enteropathy-associated T-cell lymphoma (EATL), extranodal natural killer/T-cell lymphoma (ENKTCL), and hepatosplenic T-cell lymphoma (HSTCL).

epidemiology

PTCLs are uncommon and heterogeneous malignant lymphoproliferative disorders that originate from post-thymic (peripheral) T cells or mature natural killer (NK) cells. They represent 10%–15% of all non-Hodgkin's lymphomas. Nodal subtypes are the most frequent in Caucasian patients (>80% of PTCL in Europe, PTCL-NOS 34%, AITL 28%, ALCL ALK+ 6%, ALCL ALK− 9%) [2]. In Asia, the PTCL incidence is higher due to the endemic occurrence of the Epstein-Barr virus (EBV)-associated ENKTCL (44% of PTCL in Asia excluding Japan, where there is a relatively higher frequency of adult T-cell leukaemia/lymphoma) [2]. EATL is more frequent in Northern Europe (9%–10% as compared with 1%–2% in Asia) [2], where there is a higher occurrence of human leukocyte antigen (HLA) haplotypes associated with coeliac disease. Other PTCL subtypes have been associated with chronic autoimmune disorders, such as HSTCL to Crohn's disease [3]. In PTCL, the male/female ratio is 2:1 and the median age at diagnosis is between the sixth and seventh decades of life, but both sex and age patterns vary according to different subtypes [2, 4, 5]. The ALCL ALK+ subtype has a better prognosis than the other PTCL entities, including its ALK−counterpart [6]. Recent reports have suggested that the prognostic difference between ALCL ALK+ and ALCL ALK− may at least be partly due to age-related differences (ALK+ patients are generally younger than the other PTCL patients) [7]. HSTCL occurs most frequently in younger to middle-aged males in the setting of immunosuppressive treatment [8].

diagnosis

A PTCL diagnosis should be made by an expert haematopathologist and should, whenever possible, rely on an excisional tumour tissue biopsy that provides enough material for formalin-fixed samples. According to the WHO classification (2008), the distinction among different PTCL entities requires the integration of the clinical picture, morphology, immunohistochemistry, flow cytometry, cytogenetics, and molecular biology [3]. In PTCL, the indication of the neoplastic nature of a given T-cell population is based on (i) morphology, (ii) aberrant T-cell phenotype, and (iii) clonally rearranged T-cell receptor (TCR) genes (αβ versus γδ genotypes) [9].

Table 1 summarises the immunophenotype of the PTCL entities covered by the present guidelines along with their TCR rearrangement features and putative cell of origin. Accumulating evidence indicates that information on TCR and the cell of origin plays an important role in both tumour biology and clinical behaviour, underscoring the clinical relevance of this information in the light of an increasing number of targeted therapeutic options. TIA1, granzyme B and perforin suggest a cytotoxic profile, which may imply a more aggressive clinical behaviour in PTCL-NOS [10]. At least three of the following markers: CD10, Bcl6, CXCL13, PD1, SAP, ICOS, and CCR5 are suggestive of a follicular T-helper (FTH) cell origin [9, 11, 12]. Although FTH cells are considered to be the cell of origin in AITL, this diagnosis should also be based on morphological parameters such as hyperplasia of follicular dendritic cells (FDCs), arborising high endothelial

Correspondence to: ESMO Guidelines Committee, ESMO Head Office, via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

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Table 1. Nodal and extranodal PTCL subtypes—cell of origin and related phenotypes (adapted from [9])

	PTCL entity	Immunophenotypic features	TCR	Presumed cell of origin
Nodal	PTCL-NOS	CD4>CD8, frequent antigen loss (CD5, CD7), CD30+/−, CD56+/−, subset FTH features, cytotoxic granules+/−	αβ, rarely γδ	Variable, mostly T-helper cell
	AITL	CD4+, CD10+/−, BCL+/−, CXCL13+, PD1+, ICOS+/−, SAP+/, CCR5+/−, hyperplasia of FDC, EBV+ B blasts	αβ	FTH
	ALCL ALK+	ALK+, CD30+, EMA+, CD25+, cytotoxic granules+, CD4+/−, CD3+/−	αβ	Cytotoxic T-cell
	ALCL ALK-	ALK−, CD30+, EMA+, CD25+, cytotoxic granules+, CD4+/−, CD3+/−	αβ	Cytotoxic T-cell
Extranodal	EATL, type 1	CD8(+)/−, CD56−, HLA-DQ2/-DQ8	αβ	Intra-epithelial T cells (αβ), pre-existing enteropathy
	EATL, type 2	CD8+, CD56+, HLA-DQ2/-DQ8	γδ or αβ	Intra-epithelial T cells or NK, no pre-existing enteropathy
	NKTCL	CD2+, CD56+, surface CD3−, cytoplasmic CD3ε+, gr B+, TIA-1+, perforin+, EBV+, LMP1	TCR in germline configuration, rarely αβ or γδ	NK, rarely cytotoxic T cells
	HSTCL	CD3+, CD56+/−, CD4−, CD8+/−, CD5−, TIA1+, gr M+, gr B−, perforin−	γδ, rarely αβ	Cytotoxic T cell of the innate immune system

PTCL, peripheral T-cell lymphomas; PTCL-NOS, PTCL-not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALCL ALK+, anaplastic large-cell lymphoma anaplastic lymphoma kinase positive; ALCL ALK-, ALCL anaplastic lymphoma kinase negative; EATL, enteropathy-associated T-cell lymphoma; NKTCL, natural killer/T-cell lymphoma; HSTCL, hepatosplenic T-cell lymphoma; FTH, follicular T helper; FDC, follicular dendritic cell; EMA, epithelial membrane antigen; HLA, human leukocyte antigen; EBV, Epstein-Barr virus; TCR, T-cell receptor; NK, natural killer.

venules and a substantial B-cell component, including EBV-infected B-cell blasts [13]. ENKTCL cases show intra-cytoplasmic CD3 (ε-chain), in contrast to other PTCL subtypes that only express CD3 on the cell surface [3]. CD56 is helpful in differentiating between EATL type I (CD8+/CD56−) and type II (CD8−/CD56+), which is also more often γδ+ and is not associated with coeliac disease [3]. CD30 plays a central role in the recognition of ALCL. ALCL is systematically PAX5-negative, frequently epithelial membrane antigen (EMA)-positive and, in one-third of the cases, CD45-negative. It is further categorised as ALK+ or ALK− depending on the occurrence or lack of occurrence of the classical t(2;5) translocation (or one of its variants) [3, 9]. CD20 and PAX5 allow for the identification of B-cell components and can help in distinguishing ALCL ALK− from morphologically aggressive classical Hodgkin's lymphoma (PAX5+) with anaplastic features. CD21 is useful in revealing the content of FDCs in AITL; CD68 visualises the histiocytic component that can occasionally outnumber the neoplastic cell population (e.g. lymphoepithelioid PTCL-NOS, Lennert's variant and the lymphohistiocytic variant of ALCL). The assessment of EBV (Epstein-Barr encoding region [EBER] *in situ* hybridisation) is important in T-cell malignancies, as some of the entities (e.g. ENKTCL and a subset of PTCL-NOS) show EBER positivity in the neoplastic cells.

staging and risk assessment

A complete blood count, routine blood chemistry including lactate dehydrogenase (LDH), and uric acid as well as screening tests for HIV, HTLV-1, and hepatitis B and C are required. At baseline, patients should have at least a computed tomography (CT) scan of the chest and abdomen, as well as a bone marrow aspirate and biopsy. ^{18}Fluorodeoxyglucose positron emission tomography combined with computed tomography (^{18}F-FDG PET/CT) is increasingly used in nodal PTCL at baseline and re-staging, but its role at the subtype-specific level still needs further elucidation. PET may be useful for detecting residual disease at the end of treatment, although residual FDG-avid lesions lack specificity and biopsy confirmation is recommended. The use of PET/CT is recommended in ENKTCL, where it is documented to be a valuable modality for staging and treatment planning [14–18].

prognostic indices

The International Prognostic Index (IPI) [19] is the most commonly used prognostic tool in nodal PTCL. A prognostic index for PTCL-NOS [20] with later modification [21] has been proposed, but does not univocally appear to be more useful than the original IPI [4, 22]. For clinical practice purposes, the IPI is therefore still the recommended tool. Male sex has been reported as an adverse prognostic factor [5, 23]. In ENKTCL, high EBV-DNA copy number is correlated with tumour load and is an adverse outcome predictor [24].

treatment

nodal PTCL (PTCL-NOS, AITL, ALCL ALK+, ALCL ALK−)

first-line treatment. Treatment strategies should be adapted according to factors such as age, IPI, and co-morbidity that

define a patient's eligibility for dose-intensified approaches. Whenever possible, inclusion in a clinical trial is recommended. A treatment algorithm for newly diagnosed PTCL is shown in Figure 1A. Cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone (CHOP), or variants of it, has been the most commonly used regimen in nodal PTCL. In patients less than 60 years of age with ALCL ALK+ histology, CHOP with the addition of etoposide (CHOEP) has shown some outcome benefits in terms of event-free but not overall survival (OS). CHOEP was mostly feasible in younger patients (≤60 years), toxicity being a limiting factor in older patients [25]. In a large cohort of treatment-naïve PTCL patients, a schedule of 6 courses of bi-weekly CHOEP followed by autologous stem-cell transplantation (autoSCT) demonstrated an overall response rate (ORR) of 82%, with 51% achieving a complete response (CR) [23]. At a median follow-up of 4.5 years, the three included nodal PTCL entities had an estimated 5-year OS and a progression-free survival (PFS) of 70% and 61% (ALCL ALK−), 52% and 49% (AITL) and 47% and 38% (PTCL-NOS). Recent population-based data also indicate that upfront autoSCT in chemosensitive patients is associated with improved OS [5]. On the basis of these data, a dose-dense CHOEP schedule followed by autoSCT in chemosensitive and transplant-eligible patients represents an evidence-based approach adoptable outside of a clinical trial [III, B] (Figure 1A).

Other induction regimens have been tried, e.g. platinum and gemcitabine combinations. In newly diagnosed patients, a recent phase II trial testing the PEGS regimen (cisplatin, etoposide, gemcitabine, and methylprednisolone) revealed a disappointing ORR of 39% and a 2-year PFS of only 14% [26]. Therefore, although the role of anthracyclines in PTCL is still debated, anthracycline-void regimens have, so far, failed to demonstrate their superiority to CHOP/CHOEP as the standard chemotherapy regimen outside clinical trials. In low-risk (low-/low-intermediate IPI) ALCL ALK+ patients, consolidation with autoSCT is not recommended, since these patients seem to have a more favourable outcome compared with other PTCL subtypes, with a 5-year failure-free survival (FFS) of 60%–80% [6]. The few patients with truly localised (stage I) disease should receive a shortened chemotherapy schedule (e.g. 3 courses), followed by local radiotherapy, since retrospective analyses seem to indicate a survival advantage for a combined modality approach in early stage disease [27–29] (see 'Radiotherapy' section). Frail patients not eligible for intensive chemotherapy schedules may be considered for less toxic approaches such as monotherapy schedules, e.g. with gemcitabine [30] or bendamustine [31].

relapse. Although a fair number of patients with nodal PTCL are chemosensitive, their response duration is often short and relapses are frequent. Except for CD30+ ALCL, there is no standard of care for relapsed/refractory nodal PTCL. The only globally approved salvage treatment in PTCL is the anti-CD30 antibody conjugate brentuximab vedotin (BV) administered in the setting of relapsed systemic ALCL (regardless of the ALK status). In a pivotal phase II study, BV monotherapy in heavily pre-treated, noncutaneous ALCL patients yielded an ORR of 86% and a CR rate of 57%, with a median response duration of 12.6 months [32]. Anti-CD30-directed BV monotherapy in relapsed/refractory ALCL is, therefore, evidence-supported and recommended [III, A]. This treatment may also be useful to bridge eligible patients towards allogeneic stem-cell transplantation (alloSCT). A proposed treatment algorithm is summarised in Figure 1B. For relapsed/refractory nodal PTCL other than ALCL, inclusion into clinical trials is highly encouraged. Outside clinical trials, in fit patients, combination chemotherapy regimens such as DHAP (dexamethasone, high-dose cytarabine, cisplatin) or ICE (ifosphamide, etoposide, carboplatin) can be attempted in chemosensitive patients with an available donor, aiming at alloSCT as a potentially curative modality. In unfit patients, monotherapy with gemcitabine or bendamustine are generally well-tolerated, with an ORR of approximately 50% but with modest durations of response [30, 31]. Promising new drugs are under current evaluation in clinical trials. Of these new compounds, the anti-folate pralatrexate and the histone deacetylase inhibitors romidepsin and belinostat, have recently been conditionally approved in the US, based on phase II trial results [33, 34]. The same is the case for the anti-CCR4 antibody mogamulizumab, whose label in Japan has recently been extended from adult T-cell leukaemia/lymphoma to cover also relapsed/refractory PTCL and transformed mycosis fungoides [35]. Phase III studies are ongoing in the upfront setting for all of these new compounds.

EATL

first-line treatment. In EATL, outcome after standard CHOP chemotherapy is generally poor. Recent reports indicate that, for patients sufficiently fit to tolerate more aggressive chemotherapy regimens, outcome can be significantly improved. A regimen with ifosphamide, vincristine, etoposide, and methotrexate (IVE/MTX) followed by autoSCT has shown promising results, with 5-year OS and PFS of 60% and 52%, respectively [36]. In addition, CHOEP-14 consolidated with autoSCT has shown improved outcomes compared with standard CHOP [III, B] [23]. In a European Society for Blood and Marrow Transplantation-based registry study, 4-year OS and PFS for EATL patients receiving intensive induction regimens followed by autoSCT in first CR/partial response (PR) were 59% and 54%, respectively [37]. It is difficult to estimate the proportion of all EATL patients amenable to intensive therapies, but at least one-half of the patients aged <70 years may be considered for standard-dose chemotherapy. If these patients respond to therapy, their performance status may improve, thus allowing for subsequent autoSCT.

relapse. No evidence-based specific relapse regimen can be recommended in relapsed/refractory EATL. Therefore, considerations similar to those described for 'nodal entities' (see above) are also applicable to relapsed/refractory EATL. In transplant-eligible patients who retain chemosensitivity at relapse and have a suitable donor, alloSCT should be attempted.

ENKTCL

first-line treatment. The treatment strategy for this subtype of lymphoma is unique in the context of PTCL. L-asparaginase-containing regimens such as SMILE (dexamethasone, methotrexate, ifosphamide, L-asparaginase, etoposide) and AspaMetDex (L-asparaginase, methotrexate, dexamethasone) have produced promising results [38, 39]. Anthracycline-based regimens (CHOP or CHOP-like) are not effective [40]. Addition of radiation to

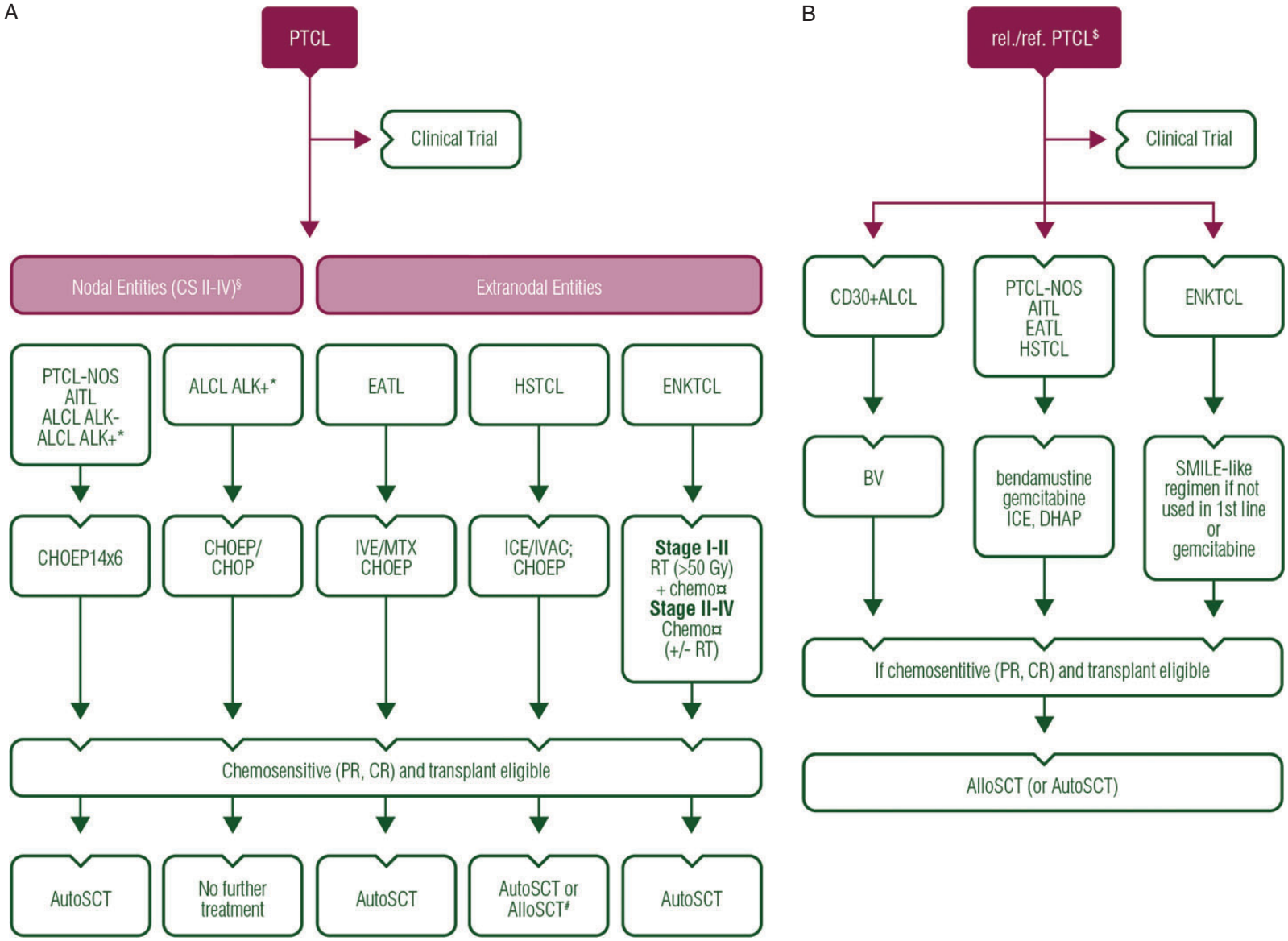

Figure 1. Integrated management algorithm (according to, e.g. risk factors, stage and histological subtype) in the (A) front-line and (B) relapsed/refractory setting. (**A**) § Stage I: shortened chemotherapy schedule (e.g. 3 courses) followed by curatively intended RT (see 'Radiotherapy' section). *ALCL ALK+ with a high-risk profile (e.g. IPI >2) should be considered for autoSCT consolidation, while autoSCT in low risk profile patients is not recommended. # if donor available. ¤ SMILE or AspaMetDex. (**B**) $: Pralatrexate and romidepsin: FDA but not EMA approved. PTCL, peripheral T-cell lymphomas; PTCL-NOS, PTCL-not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALCL ALK+, anaplastic large-cell lymphoma anaplastic lymphoma kinase positive; ALCL ALK-, ALCL anaplastic lymphoma kinase negative; EATL, enteropathy-associated T-cell lymphoma; HSTCL, hepatosplenic T-cell lymphoma; ENKTCL, extranodal natural killer/T-cell lymphoma; CHOEP, cyclophosphamide, hydroxydaunorubicin, vincristine, etoposide, prednisone; CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; IVE/MTX, ifosfamide, vincristine, etoposide/methotrexate; ICE, ifosphamide, etoposide, and carboplatin; IVAC, ifosphamide, cytarabine, etoposide; PR, partial response; CR, complete response; alloSCT, allogeneic stem-cell transplantation; autoSCT, autologous stem-cell transplantation; rel/ref, relapsed/refractory; BV, brentuximab vedotin; DHAP, dexamethasone, high-dose cytarabine, cisplatin; SMILE, dexamethasone, methotrexate, ifosphamide, L-asparaginase, etoposide; CS, clinical stage; RT, radiotherapy.

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chemotherapy is the preferred treatment of localised disease [40]. EBV DNA copy number from plasma or whole blood can be used as a biomarker for response; therefore, serial monitoring of EBV DNA copy number is recommended [15]. ENKTCL is FDG-avid, and although the role of PET/CT for response evaluation is not yet fully clarified, PET/CT is the recommended imaging modality in ENKTCL.

stages I–II. Most patients present with stage I–II nasal disease. In these cases, radiation combined with chemotherapy is the preferred treatment [40, 41]. Concurrent chemoradiotherapy and sequential chemotherapy with L-asparaginase-containing regimens followed by radiation appear to have comparable efficacy [III, A]. A radiation dose >50 Gy is recommended when treating with radiation alone. However, with radiosensitisers such as cisplatin, a weekly dose of ~40 Gy can give a comparable outcome. Central nervous system prophylaxis is not recommended, although the disease involves nasal and/or paranasal areas. Instances of localised disease outside the nasal region are rare. If feasible, radiation with or without chemotherapy seems to be a more effective treatment compared with chemotherapy alone. The role of high-dose chemotherapy followed by haematopoietic stem-cell transplantation (HSCT) is still controversial. For elderly and/or frail patients, radiation alone is recommended.

stages III–IV. L-asparaginase-containing chemotherapy regimens should be preferred as front-line treatment [III, A]. If complete remission is achieved, high-dose chemotherapy with HSCT is recommended. AutoSCT is preferable due to higher treatment-related mortality after alloSCT. For elderly and frail patients, L-asparaginase single agent or mild chemotherapy regimens (AspaMetDex or dose-modified SMILE) can be recommended [42].

relapse. A repeated pre-therapeutic biopsy is strongly recommended, since some of the PET-positive lesions can represent inflammatory changes secondary to ulceration. Selection of a salvage regimen depends on the type of primary treatment and response duration. In early relapse (<12 months) after anthracycline-based prior treatment, L-asparaginase-containing regimens should be recommended. For patients who received L-asparaginase regimens upfront, a gemcitabine-based (e.g. GELOX, gemcitabine, L-asparaginase, oxaliplatin) regimen can be considered for salvage treatment [41]. Although transplant-specific data are very limited, either auto- or alloSCT should be considered in transplant-eligible patients. Both modalities should preferably be tested in clinical trials.

HSTCL

first-line treatment. HSTCL has one of the worst prognoses among PTCLs, with 5-year FFS and OS rates of less than 10%. All cases should be treated with chemotherapy at diagnosis. Although most patients have only brief responses to anthracycline-based therapy, limited evidence suggests that they may respond to a platinum/cytarabine-based induction regimen. In the case of chemosensitivity to induction therapy, upfront consolidation with auto- or alloSCT should be offered to all eligible patients, since it may offer the only chance for durable remission [8, 43]. Recently, intense regimens such as ICE, IVAC (ifosphamide, cytarabine, etoposide), or dose-dense CHOEP/EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) have been proposed and auto- or alloSCT consolidation in fit patients is recommended [IV, B] [23, 44].

relapse. No evidence-based specific relapse regimen can be recommended in relapsed/refractory HSTCL. If chemosensitivity is achieved by current relapse regimens, alloSCT should be attempted in eligible patients, since a graft-versus-host effect has also been described in relapsed/refractory disease.

radiotherapy

PTCL seem to be somewhat less radiosensitive than the aggressive B-cell lymphomas [45], and higher radiation doses may be needed, although still lower than for most solid tumours.

front-line treatment

Most types of PTCLs usually present with advanced disease. The few patients with localised disease may be treated with local radiotherapy after chemotherapy [27–29], although no randomised evidence regarding this approach exists. Recommended doses are 30–40 Gy [46]. Because of the somewhat lower radiosensitivity of PTCLs, doses of 40 Gy should be preferred, in particular if residual lymphoma is present after chemotherapy. The treated volume should include only the initially involved volume with appropriate margins for uncertainty, according to the principles of involved site radiotherapy (ISRT) [47]. High-quality imaging before chemotherapy should be obtained in order to allow for optimal planning of subsequent radiotherapy. Modern advanced radiation treatment techniques should be used to minimise long-term toxicity [47].

ENKTCLs have special features. They most commonly involve the nasal cavity, paranasal sinuses, and Waldeyer's ring. Radiotherapy is an important part of the treatment and should be administered early [III, A] [15, 48]. Patients with stage I disease may be treated with radiotherapy alone to a dose of ≥50 Gy [49]. Alternatively, and for patients with risk factors or stage II disease, concomitant chemoradiotherapy with a platinum-containing regimen and radiotherapy dose of ≥50 Gy is an option [41]. With more effective chemotherapy regimens, sequential chemoradiation with radiation doses of 45–50 Gy may be used. ENKTCL is often locally destructive and may infiltrate extensively in the submucosa of the upper aerodigestive tract. A generous ISRT volume is recommended, covering the entire organ(s) involved with lymphoma before chemotherapy plus adjacent structures with concern for subclinical disease. Advanced imaging including PET/CT and magnetic resonance imaging and conformal radiotherapy techniques should be used.

relapse/refractory disease

Palliative radiotherapy may be used to treat locally symptomatic disease. Usual palliative doses of 30 Gy in 10 fractions may be used.

autologous stem-cell transplantation (autoSCT)

front-line treatment

There are no randomised prospective studies to guide clinicians in the decision on whether to perform autoSCT consolidation in first remission versus expectant observation. A body of prospective literature has accumulated that evaluates an up-front autoSCT in PTCL [23, 50–52]. Recent population-based data also indicate that upfront autoSCT in chemosensitive patients is associated with improved OS [5]. The nodal entities (PTCL-NOS, AITL, and ALCL mostly restricted to ALK− cases) represent the majority of patients enrolled in clinical trials. ALCL ALK+ patients usually have been excluded from upfront autoSCT trials, given their superior outcome following CHOP or CHOP-like regimens. The largest prospective study evaluating autoSCT consolidation in de novo PTCL was carried out by the Nordic group, where patients achieving CR or PR after a CHOEP-based dose-dense induction schedule received BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning and autoSCT. With the caveat of phase II data, autoSCT in first remission seems quite feasible and possibly beneficial in the selected subset of transplant-eligible PTCL [III, B].

allogeneic stem-cell transplantation (alloSCT)

AlloSCT is a potentially curative option for patients affected by PTCL. The first prospective phase II results demonstrated sustained responses in relapsed/refractory PTCL patients, suggesting the existence of a possible 'graft-versus-T-cell lymphoma' effect [III, B] [53, 54]. Non-relapse mortality (NRM) was low, supporting the feasibility of a reduced-intensity conditioning alloSCT (RIC-alloSCT) even in heavily pre-treated patients. Retrospective and registry-based analyses also confirmed that alloSCT can yield long-term responses in relapsed/refractory PTCL [55–58]. In extranodal subtypes data are anecdotal, but generally supportive of the feasibility and efficacy of alloSCT. In a recently reported prospective trial carried out in treatment-naïve PTCL patients, after an induction phase with intensive chemoimmunotherapy, responding patients were randomised to auto- or alloSCT based on the availability of a HLA identical sibling or a matched unrelated donor [59]. The sample size did not allow identification of a preferred approach among the two; however, allo- and autografted patients had a 4-year PFS of 69% and 70%, respectively. In conclusion, alloSCT is a valid treatment option in transplant-eligible relapsed PTCL patients, also after a failed prior autograft. The benefit is most evident in chemosensitive patients. A RIC-alloSCT should be preferred to a myeloablative approach in order to reduce NRM. In the upfront setting, alloSCT should be carried out primarily within clinical trials.

relapsed/refractory disease

For patients with relapsed/refractory PTCLs, potential curative options include consolidation with either an autoSCT or alloSCT. Although often appropriately offered, not all patients are able to have a transplant due to highly refractory and progressive disease. The literature remains controversial with regard to the long-term outcomes with autoSCT in this setting [60].

personalised medicine

Two personalised approaches are currently widely accepted and formally approved in the treatment of PTCL. One is the use of L-asparaginase in the treatment of ENKTCL and the other is the use of the anti-CD30 antibody conjugate BV for the treatment of relapsed/refractory ALCL also with the purpose of bridging eligible patients to alloSCT. BV is also currently being tested as part of the upfront treatment in CD30-positive PTCL other than ALCL. Increasing knowledge of the molecular mechanisms involved in PTCL pathogenesis is accumulating. This may lead to new and more targeted treatment approaches in the near future. Currently, no evidence-based personalised medicine approaches are available for patients with PTCL-NOS, AITL, EATL, and HSTCL. In these settings, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

response evaluation and follow-up

In systemic PTCL, a midway interim evaluation should be carried out in order to assess chemosensitivity. Increasing evidence points at PTCL as consistently FDG-avid tumours [61, 62] providing the rationale for the use of PET/CT, particularly in the context of residual disease evaluation. Diagnostic imaging (CT or PET/CT) should be repeated at the end of treatment along with a bone marrow biopsy (only if initially involved). Presently, no evidence-based recommendation is possible with regard to the length of follow-up. However, in the Nordic NLG-T-01 trial, where a cohort of 160 evaluable systemic PTCL patients were followed over a median period of 5 years (range: 2–8 years), 7% of all relapses occurred after 2 years [23]. On this basis, a follow-up schedule consisting of history and physical examination every 3 months for 1 year, every 6 months for 2 more years, and then once a year for detection of secondary tumours or other long-term side-effects [V, C]. CT examinations at 6, 12, and 24 months after the end of treatment are usual practice, but there is no definitive evidence that routine imaging in patients in complete remission provides any outcome advantage [V, C]. Routine surveillance with PET scan is not recommended.

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Table 2. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

FA has reported Scientific advisory boards and speaker's honoraria: Takeda, Norpharma, Kyowa Kirin, CTI Life Sciences,

Table 2. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [63].

Seattle Genetics, Infinity. Research support: Sanofi, Amgen. PG has reported Scientific advisory boards and speaker's honoraria: Takeda. LT has reported Research grants from Sanofi, Amgen, Roche and Mundipharma. WSK: Research supported by grants from Takeda, Novartis, Celgene, Roche. LS has reported Scientific advisory board and speaker's honoraria: Takeda. PC has reported Scientific advisory boards and speaker's honoraria: Takeda, Celgene, Roche, Novartis, Sanofi, Gilead, Janssen. ML has reported honoraria from Celgene, Janssen-Cilag, Roche, Amgen, Mundipharma and Teva; research contracts from Celgene, Pfizer, Mundipharma and Roche; funds received from Amgen, Roche and Takeda. MBP has reported no conflicts of interests.

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