International Journal of Hematology (2025) 122:165–171
https://doi.org/10.1007/s12185-025-04018-9

GUIDELINE

JSH practical guidelines for hematological malignancies, 2023: II. Lymphoma 7. Peripheral T-cell lymphoma (PTCL)

Dai Maruyama[1] · **Makoto Yoshimitsu**[2]

Received: 29 April 2025 / Revised: 29 April 2025 / Accepted: 19 May 2025 / Published online: 12 June 2025

Overview

The 2017 WHO Classification lists approximately 30 disease entities under the category of mature T-cell and natural killer (NK) cell neoplasms.[1] These are rare forms of lymphoma that account for 7% (slightly below 10% in Japan) of all lymphomas.[2] A global retrospective observational study on peripheral T-cell lymphoma (PTCL) conducted by the International T-cell Lymphoma Project found that the most prevalent entities in Western countries were PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), ALK-positive anaplastic large cell lymphoma (ALCL), and ALK-negative ALCL.[3] This chapter covers these four entities. Two other PTCL entities common in Japan, adult T-cell leukemia-lymphoma (ATL) and extranodal NK/T-cell lymphoma, nasal type (ENKL), will be covered in another chapter of these guidelines. Cutaneous T-cell lymphoma will not be covered in this chapter because it has its own set of guidelines.[4]

Rare entities that accounted for < 5% of all mature T/NK-cell neoplasms in the International T-cell Lymphoma Project include enteropathy-associated T-cell lymphoma (EATL), primary cutaneous ALCL, hepatosplenic T-cell lymphoma (HSTL), and subcutaneous panniculitis-like T-cell lymphoma.[3] In the 2017 WHO Classification, EATL unrelated to celiac disease, which was referred to as EATL type II in the 2007 WHO Classification, was moved to an independent category as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). HSTL, an entity derived from cytotoxic T cells (typically γδ T cells), is characterized by marked hepatosplenomegaly, typically without lymphadenopathy. Both MEITL and HSTL are often clinically progressive and have a poor prognosis with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) or CHOP-like regimens.[1]

In addition, the 2017 WHO Classification newly added follicular T-cell lymphoma (FTCL) and nodal PTCL with the T follicular helper (TFH) phenotype as nodal lymphomas of TFH cell origin in the section of AITL.[1] These were previously diagnosed as AITL or PTCL-NOS, but became new entities based on findings of characteristic genomic abnormalities in T-cell neoplasms originating from TFH cells. However, entity-specific treatments have not yet been established, and these entities are still treated as AITL or PTCL-NOS.

As in other lymphomas, the Lugano classification is used as staging and response assessment criteria.[5] Most PTCL entities are ^{18}fluoro-2-deoxyglucose (FDG)-avid, with a high rate of FDG uptake on positron emission tomography (PET),[6] which makes FDG-PET/CT useful for both staging and response assessment. The International Prognostic Index (IPI) is a useful prognostic model, and the Prognostic Index for PTCL-U (PIT) has been created for PTCL-NOS. The PIT consists of four unfavorable prognostic factors: age > 60 years, performance status > 1, serum LDH level > institutional upper limit of normal, and bone marrow involvement.[7] These models have been primarily shown to predict prognosis in patients treated with CHOP or a CHOP-like regimen, but are not used for risk stratification.

References

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✉ Dai Maruyama
dai.maruyama@jfcr.or.jp

[1] Department of Hematology Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31, Ariake, Koto-ku, Tokyo 135-8550, Japan

[2] Department of Hematology and Rheumatology, Kagoshima University Hospital, Kagoshima City, Kagoshima, Japan

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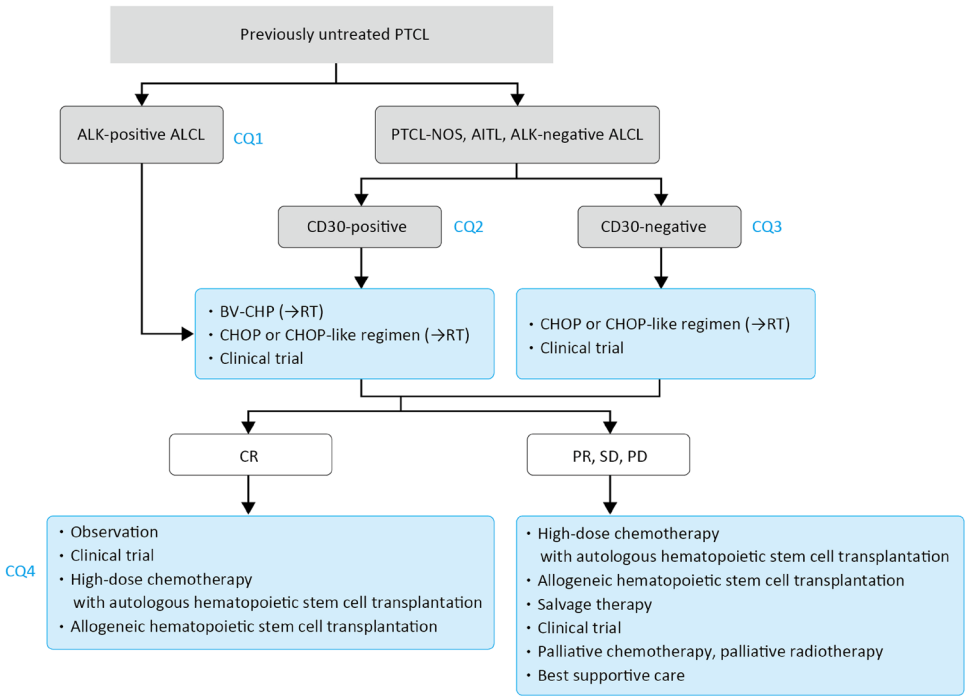
Algorithm



As noted in the Overview section, this chapter covers four disease entities: PTCL-NOS, AITL, ALK-positive ALCL, and ALK-negative ALCL. PTCL is an aggressive lymphoma (intermediate- to high-grade lymphoma) that progresses in a matter of months if left untreated, and thus all diagnosed patients are generally considered candidates for treatment. The clinical development strategy for PTCL once mirrored that for other aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL), but split off after the introduction of the anti-CD20 monoclonal antibody rituximab. A global retrospective study conducted before the introduction of rituximab showed that all PTCL entities besides ALCL had a poorer prognosis than DLBCL.[1] A study in the International T-cell Lymphoma Project showed that among PTCL patients treated with CHOP or CHOP-like regimen, those with ALK-positive ALCL had better prognosis (5-year overall survival [OS] rate: 70%), PTCL-NOS and AITL had a similarly poor prognosis (32%), and ALK-negative ALCL had an intermediate prognosis (49%).[2] Therefore, the treatment strategy for PTCL has been split into two groups: ALK-positive ALCL and all other PTCL entities.

As noted above, ALK-positive ALCL is considered to have a better prognosis among PTCL entities. In ALCL, tumor cells strongly express CD30. A phase III trial (ECHELON-2) of CHOP versus brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisolone (BV-CHP) for CD30-positive PTCL showed that BV-CHP was significantly superior to CHOP in terms of progression-free survival (PFS) and OS.[3] Consequently, BV-CHP is recommended for ALK-positive ALCL patients with an IPI score of 2 or higher, which was the population studied in the ECHELON-2 trial

(CQ1). Although the recommended treatment for ALK-positive ALCL patients with an IPI score of 0 or 1 is still CHOP or a CHOP-like regimen, BV-CHP therapy is another option (CQ1). For PTCL-NOS, AITL, and ALK-negative ALCL as well, BV-CHP therapy is recommended for CD30-positive patients based on results of the ECHELON-2 trial (CQ2). However, a subgroup analysis by entity in the ECHELON-2 trial showed no superiority to addition of brentuximab vedotin in PTCL-NOS or AITL, and thus CHOP or CHOP-like regimen remains an option for CD30-positive patients with PTCL-NOS or AITL (CQ2). For CD30-negative patients, CHOP or CHOP-like regimen is still recommended because these regimens have the greatest amount of outcome data available (ALK-negative ALCL is not included in CQ3 because CD30 positivity is a defining feature of ALCL). However, participation in a clinical trial for the development of standard therapy aimed at improving treatment outcomes is recommended because treatment outcomes for these entities are still not satisfactory (CQ3). Addition of local radiotherapy is another option for localized disease (CQ1–3). Observation is recommended after first complete response (CR) of newly diagnosed PTCL. As the significance of high-dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT) after first CR is unclear, it should preferably be performed as part of a clinical trial and not in routine practice (CQ4). For patients with a partial response (PR) or worse to first-line therapy, autologous HSCT, allogeneic HSCT, and salvage therapy (combination chemotherapy or monotherapy) are the main options in general practice settings, but evidence for these options is lacking. Therefore, participation in a clinical trial is also recommended. Intensive chemotherapy may not be indicated in some cases due to poor performance status, organ damage, or patient preference; in such cases, palliative chemotherapy, palliative radiotherapy, and best supportive care are options.

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CQ1 What treatments are recommended for previously untreated ALK-positive ALCL?

Recommendation grade: Category 1
Brentuximab vedotin plus CHP (BV-CHP) is recommended.

Explanation

ALK-positive ALCL characteristically has a t(2;5)(p23:q35) chromosomal translocation, resulting in a chimeric gene of the nucleophosmin gene (*NPM1*) and the *ALK* gene, that is involved in its pathogenesis. Its diagnosis requires detection of CD30 antigen expression in tumor cells. ALK-positive ALCL accounts for only 3% of all non-Hodgkin lymphomas, but up to 10–20% of lymphomas in children.[1] Most cases are advanced, with an IPI score of 2 or higher. CHOP and CHOP-like regimens have been shown to yield a 5-year OS rate of 70%.[2,3] Five-year OS rates by IPI risk score are 90% for 0 or 1, 68% for 2, 23% for 3, and 33% for 4, with a particularly good prognosis in the low-risk group.[3] For localized disease, a short course of CHOP or a CHOP-like regimen followed by additional radiotherapy is a treatment option, as it is with other aggressive lymphomas.

Brentuximab vedotin is an antibody–drug conjugate consisting of a chimeric anti-CD30 monoclonal antibody linked to the microtubule inhibitor monomethyl auristatin E (MMAE) by an enzyme-cleavable linker. A phase III trial (ECHELON-2) of CHOP versus BV-CHP for CD30-positive PTCL including ALK-positive ALCL showed that BV-CHP (6–8 cycles) was significantly superior to CHOP (6–8 cycles) in terms of PFS and OS.[4] Subgroup analysis by entity showed a favorable trend for the addition of brentuximab vedotin in ALK-positive ALCL, with a hazard ratio of 0.29 (95% CI 0.11–0.79) for PFS and 0.38 (95% CI 0.12–1.22) for OS. Consequently, BV-CHP is recommended for ALK-positive ALCL patients with an IPI score of 2 or higher, which was the population studied in the ECHELON-2 trial. BV-CHP is also recommended for ALK-positive ALCL patients with an IPI score of 0 or 1, but CHOP or CHOP-like regimen is another option. Although the ECHELON-2 trial permitted consolidative local radiotherapy when planned in advance, there is no evidence to support a treatment schedule with a shortened course of BV-CHP therapy plus local radiotherapy for localized disease.

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CQ2 What treatments are recommended for previously untreated CD30-positive PTCL-NOS, AITL, and ALK-negative ALCL?

Recommendation grade: Category 1
Brentuximab vedotin plus CHP (BV-CHP) is recommended.

Explanation

Before the introduction of the anti-CD20 monoclonal antibody rituximab for B-cell lymphomas, PTCL was treated as an aggressive lymphoma, and the treatment development for PTCL was conducted by including it in clinical trials along with other aggressive lymphomas such as DLBCL. Results of a four-arm randomized trial in the United States that compared CHOP versus intensive chemotherapy for aggressive lymphomas including PTCL established CHOP as the standard of care.[1] These results also established CHOP as the standard of care for PTCL. For localized disease, a short course of CHOP or CHOP-like regimen followed by additional radiotherapy is a treatment option, as it is with other aggressive lymphomas.

The CD30 antigen is a transmembrane glycoprotein receptor in the tumor necrosis factor receptor family. As CD30 antigen is only expressed on activated lymphocytes and some eosinophils in normal tissues, it is considered a tumor-specific antigen. By PTCL entity, PTCL-NOS and AITL have a CD30 positivity rate of 58% and 63%, respectively, on immunohistochemical staining, with a strong positivity rate of approximately 5% to 20%. In contrast, because ALK-negative ALCL is defined by CD30 antigen expression in tumor cells, it has a positivity rate of 100%, with strong positivity.[2] Brentuximab vedotin is an antibody–drug conjugate consisting of a chimeric anti-CD30 monoclonal antibody linked to the microtubule inhibitor MMAE by an enzyme-cleavable linker. A phase III trial (ECHELON-2) of CHOP versus BV-CHP for CD30-positive PTCL including ALK-positive ALCL showed that BV-CHP was significantly superior to CHOP in terms of PFS and OS.[3] Approximately 70% of all enrolled patients had ALCL. Subgroup analyses of PFS and OS by entity showed that addition of brentuximab vedotin yielded favorable outcomes in ALK-negative ALCL, but not in PTCL-NOS or AITL.[3] Five-year follow-up data from the ECHELON-2 trial showed similar results.[4] Because the ECHELON-2 trial demonstrated the superiority of BV-CHP in terms of the primary endpoint of PFS and the secondary endpoint of OS, BV-CHP was concluded to be the standard of care for first-line treatment of previously untreated CD30-positive PTCL. However, the clinical indication of BV-CHP for entities other than ALCL remains undetermined. Therefore, CHOP or CHOP-like regimen is also a reasonable choice for PTCL-NOS and AITL.

Although the ECHELON-2 trial permitted consolidative local radiotherapy when planned in advance, there is no evidence to support a treatment schedule with a shortened course of BV-CHP therapy plus local radiotherapy for localized disease.

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or AITL, only ALK-positive ALCL.[4] A phase II trial of the DA-EPOCH regimen (etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin) was conducted in Japan,[5] but its relative efficacy compared to CHOP is unknown.

In conclusion, because no standard therapy has been established for previously untreated, CD30-negative PTCL-NOS or AITL (ALK-negative ALCL is not included in this CQ because CD30 positivity is required for diagnosis), participation in a clinical trial is recommended, and otherwise CHOP or a CHOP-like regimen is recommended in general practice settings based on past outcome data.

CQ3 What treatments are recommended for previously untreated CD30-negative PTCL-NOS and AITL?

Recommendation grade: Category 2A CHOP or a CHOP-like regimen is recommended. However, participation in a clinical trial is recommended because no standard therapy has been established.

Explanation

Before the introduction of the anti-CD20 monoclonal antibody rituximab for B-cell lymphomas, PTCL was treated as an aggressive lymphoma, and the treatment development for PTCL was conducted by including it in clinical trials along with other aggressive lymphomas such as DLBCL. The results of a four-arm randomized trial in the United States that compared CHOP versus intensive chemotherapy for aggressive lymphomas including PTCL established CHOP as the standard of care.[1] These results also established CHOP as the standard of care for PTCL. For localized disease, a short course of CHOP or a CHOP-like regimen followed by additional radiotherapy is a treatment option, as it is with other aggressive lymphomas.

However, a retrospective study outside Japan and pooled analysis by the Japan Clinical Oncology Group conducted before the introduction of rituximab showed that all PTCL entities besides ALCL had a poorer prognosis than DLBCL.[2,3] These findings led to investigation of CHOP-based regimens to improve treatment outcomes for PTCL. A German clinical trial group conducted a randomized controlled trial of CHOP versus CHOP plus etoposide (CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone) in patients with aggressive lymphoma (14% had PTCL). Although a subgroup analysis in PTCL showed that CHOEP yielded superior event-free survival, further analysis by entity showed no superiority for ALK-negative ALCL, PTCL-unspecified,

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CQ4 Is high-dose chemotherapy with autologous HSCT after achievement of CR on first-line chemotherapy recommended as consolidation for patients with newly diagnosed advanced PTCL-NOS, AITL, or ALK-negative ALCL?

Recommendation grade: Category 2A

Addition of high-dose chemotherapy with autologous HSCT for patients in CR after first-line chemotherapy for newly diagnosed advanced PTCL-NOS, AITL, or ALK-negative ALCL is not recommended in general practice settings. It should preferably be performed as part of a clinical trial.

Explanation

A study by the International T-cell Lymphoma Project showed that among PTCL patients treated with CHOP or CHOP-like regimen, those with ALK-positive ALCL had the best prognosis (5-year OS rate: 70%), PTCL-NOS and AITL had a similarly poor prognosis (32%), and ALK-negative ALCL had an intermediate prognosis (49%).[1] Due to these unsatisfactory treatment outcomes, high-dose chemotherapy with autologous HSCT in first remission was investigated for its potential to improve prognosis. In a phase II trial where first-line induction chemotherapy with CHOP was followed by autologous HSCT in patients who achieved PR or better, the 3-year OS rate was 71% in autologous HSCT recipients, compared with 11% in non-recipients.[2] However, it should be noted that this was not a randomized controlled trial, and 34% of patients were unable to undergo autologous HSCT mainly due to refractoriness to first-line therapy or disease progression after induction chemotherapy, meaning that the influence of selection bias on the better prognosis observed in patients who underwent (ie, were able to undergo) autologous HSCT cannot be ruled out. Long-term outcomes are also unsatisfactory, with 3- to 5-year PFS rates ranging from 36 to 44% in all patients.[2,3] Several retrospective studies have also shown an unclear significance of autologous HSCT for PTCL patients who achieved CR on CHOP or CHOP-like regimen.[4–6] However, a prospective observational study from the United States showed that autologous HSCT after CR on CHOP or a CHOP-like regimen may improve prognosis in patients with newly diagnosed PTCL who have advanced disease, bone marrow involvement, or other high-risk features.[7] In the ECHELON-2 trial, a randomized controlled trial of CHOP versus BV-CHP for CD30-positive PTCL, responders to induction chemotherapy were permitted to undergo consolidative autologous HSCT when planned in advance. Autologous HSCT was planned in advance for 37% of all patients (n = 170).[8] Ultimately, 19% of patients (n = 88) underwent consolidative autologous HSCT,[9] and results suggested that autologous HSCT may be effective in patients who have achieved CR on BV-CHP.[10] These findings indicate that some PTCL patients may benefit from autologous HSCT after induction, and autologous HSCT is performed as general clinical practice in some Western countries. However, as no randomized controlled trial has examined the significance of autologous HSCT for patients with CR to first-line therapy, no evidence exists to support an active recommendation.

Therefore, autologous HSCT after achievement of CR on CHOP or a CHOP-like regimen as first-line therapy is not recommended in general practice settings, and should preferably be performed as part of a clinical trial.

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Data availability Not applicable.

Declarations

Conflict of interest DM has received per diem, including speaking fees, from Janssen Pharmaceutical, Chugai Pharmaceutical, Kyowa Kirin, Eisai, AstraZeneca, SymBio Pharmaceuticals, and Takeda Pharmaceuticals; and has received research funding from Novartis Pharma, Chugai Pharmaceutical, Ono Pharmaceutical, Takeda Pharmaceuticals, Janssen Pharmaceutical, MSD, Loxo Oncology, Bristol Myers Squibb, Kyowa Kirin, Otsuka Pharmaceutical, and IQVIA Services Japan. MY has no conflicts of interest to report.