Latin American Consensus for the Diagnosis, Staging, and Treatment of Peripheral T-Cell Lymphoma Not Otherwise Specified

Henry Idrobo Quintero, MD[1]; Juan Esteban Garcia-Robledo, MD[2]; Juan Alejandro Ospina, MD[3]; Humberto Martínez-Cordero, MD[4]; Lina María Martinez-Correa, MSc[5]; Maria Alejandra Torres Viera, MD[6]; Brady Ernesto Beltran, MD[7]; Luis Villela, MD[8]; Ana Carolina Oliver, MD[9]; Alana von Glasenap, MD[10]; Macarena Roa, MD[11]; German Stemmelin, MD[12]; Jose Macias, MD[13]; Perla R. Colunga-Pedraza, MD[14]; Myrna Candelaria, MD[15]; Marcela Zamora, MD[16]; Rosa Oliday Ríos-Jiménez, MD[17]; Rafael Pichardo-Rodriguez, MD[18]; Guilherme Fleury Perini, MD[19]; André Abdo, MD[20]; Danielle Leão Cordeiro de Farias, MD[21]; Denisse Castro Uriol, MD[22]; Sally Paredes-Noguni, MD[22]; Cristobal Augusto Frutos, MD[23]; Jhon Alexander Avila-Rueda, MD[24]; Ana Milena Cantillo Garcia, MD[24]; Isabel Matilde Chinchia, MD[25]; Jenny Niño-Galvis, MD[26]; Carlos Fernando Gómez-Calcetero, MD[27]; César Abad De la Hoz, MD[28]; Eleazar Hernández-Ruiz, MD[29]; Francisca Ramírez, MD[30]; Jaiver Alexander Fonseca, MD[24]; Jorge Ernesto Muñio-Perurena, MD[31]; Yamile Quintero-Sierra, MD[32]; Jose Manuel Vela-Ruiz, MD[33]; Leandro Francisco Barrios, MD[34]; Edgar Fabián Manrique-Hernández, MD[24]; Robson Ferrigno, MD[35]; Silvana Orozco, MD[36]; Jose Sandoval-Sus, MD[37]; Carlos Chiattone, MD[38]; Jorge Castillo, MD[39]; Bryan Valcarcel, MD, MPH[40]; and Luis Malpica, MD[40]

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ABSTRACT

PURPOSE Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is an aggressive, heterogeneous subtype of non-Hodgkin lymphoma with poor prognosis and limited therapeutic options. In Latin America (LATAM), management is challenged by restricted access to advanced diagnostics, higher prevalence of oncogenic viruses (Epstein-Barr virus, HTLV-1), and variable health care resources. This international consensus provides evidence-based, regionally adapted recommendations for diagnosis, staging, risk stratification, treatment, and follow-up of adult patients with PTCL-NOS.

METHODS A multidisciplinary panel of hematologists and oncologists from multiple LATAM countries, who are members of the *Grupo de Estudio Latinoamericano de Linfoproliferativos*, used a modified Delphi process (February-July 2025). An initial questionnaire of 11 items addressed diagnostic evaluation, staging, risk stratification, first-line therapy, response assessment, consolidation with stem-cell transplantation, salvage therapy, and supportive care. Consensus was defined as ≥80% agreement on a five-point Likert scale using the RAND/UCLA appropriateness method. Two rounds of anonymous voting and discussion incorporated cost-effectiveness and local resource constraints.

RESULTS Key recommendations include (1) positron emission tomography (PET)/computed tomography (CT) as preferred staging modality (with total metabolic tumor volume for prognostication) plus mandatory bone-marrow biopsy; (2) Prognostic Index for PTCL-U as primary risk-stratification tool; (3) cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone for fit patients ≤60 years with planned autologous stem-cell transplantation (ASCT), versus cyclophosphamide, doxorubicin, vincristine, and prednisone-21 otherwise; (4) brentuximab vedotin + cyclophosphamide, doxorubicin, prednisone for CD30$^+$ cases (≥10% expression); (5) interim and end-of-treatment PET/CT for response assessment; (6) ASCT in first complete remission; (7) early allogeneic transplantation referral for relapsed/refractory disease; and (8) standardized immunohistochemistry/flow cytometry panels. Resource-limited adaptations prioritize accessible strategies and encourage clinical trial participation.

CONCLUSION This LATAM-specific consensus integrates global evidence with regional realities to optimize outcomes for PTCL-NOS. Implementation should standardize care, reduce diagnostic delays, and improve equitable access to effective therapies across LATAM.

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INTRODUCTION

Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is a rare, heterogeneous, and aggressive subtype of non-Hodgkin lymphoma (NHL), defined by the WHO 5th Edition[1] and the International Consensus Classification[2] as a T-cell lymphoma that do not fit into other specific categories, accounting for 25%-30% of PTCL and characterized by poor prognosis, with 5-year overall survival (OS) rates of 20% to 40%.[3-5] The standard initial treatment is based on conventional chemotherapy, which achieves overall response rates (ORRs) between 60% and 70%.[5,6] However, relapses are frequent. PTCL-NOS biological diversity, evolving molecular classification, and limited therapeutic options pose significant challenges for diagnosis and management.[7]

In Latin America (LATAM), these challenges are compounded by restricted availability of advanced diagnostic modalities such as positron emission tomography/computed tomography (PET/CT), incomplete pathologic evaluation because of scarce immunohistochemistry (IHC) and next-generation sequencing resources, and constrained opportunities to provide novel therapies, whereas distinct epidemiologic patterns, marked by a higher prevalence of oncogenic viruses such as Epstein-Barr virus and HTLV-1, further adds to the complexity of understanding PTCL in the region.[4,7] Despite these barriers, LATAM hematologists have adapted global evidence to local contexts, prioritizing cost-effective strategies while advocating for improved access to cutting-edge treatments.[5]

This international consensus, developed through the collaborative efforts of researchers from multiple LATAM countries and advisory members, aims to provide evidence-based recommendations for the diagnosis, risk stratification, treatment, and follow-up of patients with PTCL-NOS. By synthesizing high-quality scientific evidence with regional expertise, this consensus aims to enhance clinical decision making, optimize patient outcomes, and promote participation in clinical trials to advance therapeutic innovation.

METHODS

Participants

A multidisciplinary panel of hematologists, oncologists, pathologists, and clinical researchers from various LATAM countries, supported by an independent methodological team, developed this consensus on the management of PTCL-NOS. Panel members were selected based on their expertise in T-cell lymphomas, particularly PTCL-NOS, and their availability to participate in evidence review and consensus-building activities. Declarations of interest were collected from all participants at the outset of the consensus process to ensure transparency.

Evidence Search and Formulation

The panel convened to define the scope of the consensus during an initial session. The target population was established as adult patients diagnosed with PTCL-NOS, encompassing early and advanced stages. The consensus content was organized into key domains: diagnostic evaluation (immunophenotypic profiling and IHC), staging and imaging, risk stratification, first-line treatment approach, response assessment, and consolidation strategies, including autologous stem-cell transplantation (ASCT) and allogeneic hematopoietic SCT (allo-HCT).

Delphi Process

A modified Delphi method was used to develop the consensus recommendations, with meetings held between February 2025 and July 2025. The panel formulated an initial questionnaire organized into sections corresponding to the predefined domains: diagnostics, risk stratification, first-line treatment regimen, response assessment strategies, and consolidation strategies. The questionnaire comprised 11 items, refined by the panel to ensure relevance and clarity. In the first Delphi round, all panel members evaluated the items using a five-point Likert-type scale based on the RAND/UCLA appropriateness method. Responses were anonymized, and results were analyzed to identify items achieving consensus (defined as ≥80% agreement on appropriateness). In the second round, items that lack consensus were revised, discussed, and revoted, with voting results from the first round shared to facilitate convergence. Final recommendations were formulated based on the second-round outcomes. Cost-effectiveness and access to diagnostic and therapeutic modalities were explicitly considered to ensure that recommendations are feasible in LATAM health care systems, where resource constraints are prevalent.

RESULTS

Question 1: What Is the Optimal Imaging Modality for Initial Staging?

PTCL-NOS has a heterogeneous nature which may involve nodal and extranodal sites in up to 60% of cases.[5,6] With PET/CT 18-fluorodeoxyglucose (18-FDG), around 29%-50% of patients exhibit extranodal sites undetected by CT,[9-11] showing a sensitivity of 88%-96.6% and a specificity of 98.8%-100%, an accuracy 99% for detecting extranodal disease,[12] significantly outperforming CT (sensitivity 87.5%, specificity 85.7%, accuracy 88%),[7,13] resulting in a modification of clinical stage in 23% of cases (17% upstaged and 6% downstaged).[13] Around 86%-98% of cases are 18-FDG–avid,[9,11,13] with a heterogeneous uptake range (standardized uptake value maximum of 2.8-42.3, median 12.3), lower in cutaneous involvement and higher in nodal and visceral sites.[11,12,14] For bone marrow involvement (BMI), PET/CT demonstrates high specificity (83%-90.2%) but low

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sensitivity (8%-43.2%),[15,16] limiting its ability to replace bone marrow biopsy (BMB),[16] which remains essential for patients eligible for transplantation. A guided biopsy is recommended when PET/CT reveals focal uptake outside the iliac crest.[16] High total metabolic tumor volume (TMTV) at diagnosis has emerged as a prognostic tool.[17-19] It has been shown that patients presenting with high TMTV have a 2-year progression-free survival (PFS) and overall OS rates of 26% and 50%, respectively, compared to 71% and 80% in patients with low TMTV,[20] and 4-year OS of 63% versus 90% (hazard ratio [HR], 6.03; $P = .022$).[17] According to the 2017 WHO Global Atlas, approximately 95% of low-income countries and 92% of lower-middle–income countries lack readily accessible PET/CT.[21]

Recommendations:

- PET/CT is the imaging modality of choice for initial staging and detection of extranodal disease, offering additional prognostic value through TMTV assessment.
- PET/CT does not replace BMB for detecting BMI, and BMB should remain a routine component of diagnostic workup and for patients considered for transplantation.

Question 2: What Are the Optimal Risk Stratification Scales at Diagnosis?

The International Prognostic Index (IPI) was developed in 1993,[22] designed for B-cell lymphomas, and subsequently validated for T-cell lymphomas, including PTCL-NOS.[23] In recent years, new prognostic models tailored to PTCL have emerged,[23] however, no standardized recommendations have been established for their routine use,[5] including

1. *IPI*: Incorporates five factors: age (>60 years), performance status (Eastern Cooperative Oncology Group [ECOG] ≥ 2), lactate dehydrogenase (LDH) levels (elevated), extranodal involvement (≥2 sites), and Ann Arbor stage (III/IV). Its validation in PTCL-NOS demonstrates reasonable prognostic discrimination, stratifying patients into low-intermediate-high-risk groups.[24] Its applicability is limited by its lack of specificity for PTCL-NOS.
2. *Prognostic Index for PTCL-U (PIT)*: The PIT, specifically designed for PTCL-NOS (previously termed PTCL-unspecified), includes four factors: age (>60 years), performance status (ECOG ≥ 2), elevated LDH, and BMI. Provides improved prognostic stratification compared to IPI by incorporating BMI, a frequent feature in T-cell lymphomas.[25] Its reliance on clinical and laboratory parameters may overlook molecular heterogeneity.
3. *Age-Adjusted IPI (a-IPI)*: The a-IPI is tailored for patients ≤60 years, includes stage III/IV, elevated LDH, and ECOG ≥ 2. Its application in PTCL-NOS is less robust due to the limited incorporation of T-cell–specific prognostic factors, reducing its discriminative power in this subtype.[24]
4. *Modified Prognostic Index for PTCL-U (mPIT)*: The mPIT integrates proliferation index Ki-67 and other molecular markers depending on the model variation. Its requirement for IHC or molecular profiling may limit its feasibility in resource-constrained settings.[26]
5. *International T-Cell Lymphoma Project (ITCLP)*: A model based on a large cohort of T-cell lymphoma patients, including PTCL-NOS, incorporates clinical features, imaging findings and molecular markers.[27] Offers superior prognostic accuracy by addressing the molecular and clinical heterogeneity of PTCL-NOS but requires advanced diagnostic capabilities, which may not be universally available.

Recommendations:

- The PIT is currently the most appropriate risk stratification scale for the variable access to advanced diagnostics, offers a balance of specificity, incorporating BMI as a T-cell-specific factor, while relying on accessible clinical and laboratory parameters.[25]
- In settings with access to advanced molecular profiling, the ITCLP model may be preferred due to its comprehensive integration of clinical, imaging, and molecular data, providing the highest prognostic accuracy.[27]

Question 3: Is the Incorporation of Etoposide Into First-Line Treatment Regimens Clinically Relevant and Beneficial?

The cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen has been the standard of care for PTCL for decades, with reported ORR of 50% and 5-year OS rates of 30%-40%.[3,8] A retrospective analysis by Schmitz et al[28] evaluated 343 patients with PTCL and natural killer (NK)-cell lymphomas treated within the prior German High-Grade Non-Hodgkin Lymphoma Study Group, of whom 176 received CHOP and 167 received cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone (CHOEP). For patients aged ≤60 years, the 3-year event-free survival (EFS) was significantly higher with CHOEP (75.4%) compared to CHOP (51%), with particularly pronounced benefits in the anaplastic lymphoma kinase–positive (ALK^+) anaplastic large cell lymphoma (ALCL) subgroup (EFS, 91% *v* 57%). However, in PTCL-NOS, the EFS difference was less marked (61% *v* 48%; $P = .057$), and no differences in OS. A Dutch registry of over 1,400 patients aged ≤60 years found that the benefit of CHOEP was no longer evident after adjusting for age, IPI score, and use of ASCT, suggesting selection bias, as CHOP was more frequently administered to less fit patients.[29,31] More intensive first-line regimens, such as dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin or mega-CHOEP, have failed to demonstrate improvements in OS and are associated with increased toxicity, rendering them non-standard in current practice.[30-32] This has also been demonstrated by our group, showing that in LATAM patients, the addition of etoposide-containing regimens did not show an increase in OS or PFS for patients with PTCL-NOS.[5] A multicenter phase 2 trial investigated CHOEP combined with brentuximab vedotin (BV), followed by BV

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consolidation, achieving a complete response (CR) rate of 79% and a 2-year PFS of 59%.[33]

Recommendations:

- Due to consistent improvements in CR and EFS, CHOEP may be considered a viable option for patients with good performance status, aged ≤60 years, and without significant comorbidities, particularly when consolidation with ASCT is planned. In patients aged >60 years or with comorbidities, etoposide is not recommended due to its unfavorable toxicity profile, and CHOP-21 remains the preferred regimen.
- Whenever feasible, participation in clinical trials evaluating novel therapeutic combinations with improved efficacy and reduced toxicity should be prioritized.

Question 4: Is the Addition of BV to First-Line Cyclophosphamide, Doxorubicin, and Prednisone (BV + CHP) Clinically Relevant and Beneficial?

Compared to patients with B-cell NHL, those with T-cell NHL, including PTCL-NOS, exhibit lower response rates to chemotherapy, as well as inferior PFS and OS.[3] In PTCL-NOS, CD30 expression is detected in up to 60% of cases.[34,35,37] However, IHC detection of CD30 expression lacks standardization, and it is critical to ensure that CD30 positivity is evaluated specifically in tumor cells, as opposed to inflammatory cells such as immunoblasts, which may also express CD30.[34,35] BV + cyclophosphamide, doxorubicin, prednisone (CHP) as first-line therapy for $CD30^+$ PTCL is supported by the ECHELON-2 trial, a phase 3, double-blind, randomized, placebo-controlled study conducted across 132 sites in North America, Europe, Asia, and the Middle East.[36] This trial randomized 452 patients with $CD30^+$ PTCL (expression ≥10%) to receive either BV + CHP (n = 226) or CHOP (n = 226). The median age was 58 years. ASCT was performed in 50 patients (22%) in the BV + CHP arm and 39 patients (17%) in the CHOP arm. After a median follow-up of 36.2 months (95% CI, 35.9 to 41.8), the median PFS was significantly longer in the BV + CHP arm (48.2 months [95% CI, 35.2 to not reached]) compared to the CHOP arm (20.8 months [95% CI, 12.7 to 47.6]). The 3-year PFS was 57.1% (95% CI, 49.9 to 63.7) for BV + CHP versus 44.4% (95% CI, 37.6 to 50.9) for CHOP.[36,37]

Recommendations:

- We recommend the use of the BV + CHP protocol as first-line therapy is recommended for patients with PTCL exhibiting CD30 expression ≥10%. This regimen offers clinically meaningful improvements in PFS and OS compared to CHOP, with a manageable safety profile.
- However, treatment initiation should not be delayed by waiting for this biomarker or BV availability, as real-life experience has shown that there is a significant impact in reducing the interval between diagnosis and treatment.

Question 5: Is Early Treatment Response Assessment With Interim PET/CT After 2-4 Cycles of Therapy Indicated?

Studies, primarily retrospective, suggest that a positive interim PET/CT (Deauville score >3) is associated with inferior PFS and OS.[38,39] This early assessment can identify patients with suboptimal responses, potentially allowing an escalation to high-dose chemotherapy, ASCT, or enrollment in clinical trials. Data from studies in aggressive lymphomas, including PTCL, indicate that interim PET/CT has a high negative predictive value but variable positive predictive value, particularly in T-cell lymphomas, due to false positives from inflammatory processes.[40] Additionally, the optimal timing (after two *v* four cycles) and therapeutic implications of a positive PET/CT remain under investigation, with no standardized guidelines for PTCL-NOS.

Recommendations:

- Interim PET/CT2-4 is recommended for patients with PTCL-NOS, as it provides prognostic information and facilitates early therapeutic decision-making with prompt treatment intensification or alternative strategies, such as ASCT or novel therapies, to improve outcomes. This recommendation is supported by a moderate level of evidence, primarily from retrospective studies, given the lack of prospective data specific to PTCL-NOS.[38,39]
- In resource-limited settings, such as parts of LATAM, where access to PET/CT may be restricted, the decision to perform PET/CT2-4 should weigh cost, availability, and potential clinical impact.

Questions 6: What Is the Optimal Number of Treatment Cycles and Interval for First-Line Therapy?

The recommended first-line regimens and their corresponding administration intervals are depicted in Figure 1.

Question 7: What Is the Optimal Imaging Modality for EOT Response Assessment and Follow-Up?

Recommendations:

- The preferred imaging modality for end-of-treatment (EOT) assessment is 18-FDG PET/CT utilizing the Deauville five-point scale with a positivity cutoff of >3, supported by a moderate level of recommendation, grounded in current evidence from retrospective studies, which consistently indicate that is predictive of PFS and OS, exhibits high FDG avidity with approximately 90% of cases demonstrating significant uptake.[41,42]
- Regarding routine imaging follow-up for patients with PTCL-NOS in CR1, the level of recommendation is very low. We do recommend the use of serial CT scans at 6-12-24 months, however, the evidence is lacking and the follow-up frequency has not been established with available literature. Follow-up PET/CT is not recommended.[43]

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Regimen	No. of Cycles	Dosing Interval, Days	Recommendation Status/Clinical Setting	Notes
BV-CHP (brentuximab vedotin + cyclophosphamide + doxorubicin + prednisone)	6–8	21	**Preferred for patients with CD30 expression ≥10% on tumor cells**	*Supported by ECHELON-2 trial; improves PFS and OS v CHOP in CD30+ PTCL*
CHOEP (cyclophosphamide + doxorubicin + vincristine + etoposide + prednisone)	6	21	**Preferred for fit patients ≤60 years with planned autologous SCT**	*Improves CR rate and EFS in younger fit patients; etoposide benefit most evident when ASCT consolidation is planned*
CHOP-21 (cyclophosphamide + doxorubicin + vincristine + prednisone)	6	21	**Preferred in patients >60 years, unfit patients, or resource-limited settings**	*Standard backbone when etoposide or brentuximab vedotin is not available or not tolerated; treatment should not be delayed*
CHOEP-14 (dose-dense) followed by ASCT	6 (cycles 5–6 for mobilization)	14	**Alternative only in highly selected fit patients ≤60 years at experienced centers**	*Higher toxicity; limited evidence of superiority over CHOEP-21 + ASCT*
BV-CHP followed by ASCT (in CR1)	6–8 (induction)	21	**Preferred for CD30+ patients who achieve CR1 and are transplant-eligible**	*Consolidative ASCT recommended after BV-CHP in eligible patients*
CHOEP/CHOP followed by ASCT (in CR1)	6	21	**Preferred for transplant-eligible patients who achieve CR1**	*ASCT in first complete response is recommended for eligible patients (excluding ALK+ ALCL)*
DA-EPOCH	6	21	Not routinely recommended	*No clear survival benefit over CHOEP/CHOP; higher toxicity in most studies*
Mega-CHOEP	6–8	21 (or intensified)	Not routinely recommended	*Increased toxicity without proven OS benefit in PTCL-NOS*
Hyper-CVAD alternating with intermediate-dose cytarabine	6	21	Not routinely recommended	*High toxicity; limited data in PTCL-NOS; not superior to standard regimens*
CHOP followed by IVE	1 cycle CHOP + 3 cycles IVE	21	Not routinely recommended	*Limited evidence; not considered the standard first-line approach*

FIG 1. Recommended first-line regimens for the treatment of PTCL-NOS. PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified. Recommendation status reflects the strength of evidence, toxicity profile, and feasibility in the Latin American context (including resource constraints). "Preferred" regimens are those with the best balance of efficacy and safety based on available data and expert consensus. "Alternative" options may be considered in selected patients or centers with specific expertise. Regimens marked "Not routinely recommended" are associated with higher toxicity without clear improvement in overall survival in PTCL-NOS and should generally be avoided outside clinical trials. Color key: Teal = preferred, yellow = alternative, red = not routinely recommended. ASCT, autologous stem-cell transplantation; BV-CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR1, first complete response; CVAD, cyclophosphamide, vincristine, doxorubicin (Adriamycin), and the steroid dexamethasone; DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; IVE, ifosfamide, vincristine, and etoposide; OS, overall survival; PFS, progression-free survival; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; SCT, stem-cell transplantation.

Question 8: What Is the Role of ASCT?

Given the high relapse rates and short duration of responses (DoRs) with conventional chemotherapy, consolidation with ASCT in CR1 is an accepted strategy in most international guidelines, despite the absence of phase III trials directly comparing ASCT to observation. The benefit is most evident in ALK-negative ALCL but is also observed in PTCL-NOS and angioimmunoblastic T cell lymphoma (AITL), particularly in patients with high IPI scores or advanced-stage disease.[44] Immunotherapy and targeted agents, such as BV and epigenetic modulators, show promising results but have not yet replaced ASCT as the standard consolidation approach. Chimeric antigen receptor T-cell therapies face significant

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technical and biological challenges in T-cell lymphoma histologies, limiting their current applicability.[45]

Patient selection:

- *Optimal candidates*: The greatest benefit of ASCT is observed in younger patients with good performance status, advanced-stage disease, and complete metabolic response postinduction.
- *Adverse factors*: Failure to achieve CR, advanced age, and high-risk IPI scores are associated with poorer outcomes.[44]

Recommendations:

- Consolidation with ASCT is recommended for all eligible patients with PTCL-NOS (excluding ALK-positive ALCL) who achieve CR1 postinduction.
- ASCT should be performed under optimal conditions, ensuring adequate disease control to maximize clinical benefit.

Question 9: What Is the Most Appropriate Salvage Therapy After First-Line Regimen for R/R PTCL-NOS?

There are no randomized controlled trials that have established a standard of care. The only known curative treatment approach for this relapsed/refractory (R/R) PTCL-NOS is allo-HCT, and achieving a CR increases the chances of prolonged remission and possible cure. Three recent large retrospective cohorts underscore the curative role of allo-HCT for these patients. Foley and Mehta-Shah[46] presented a large retrospective cohort that included 508 US patients diagnosed with different types of T-cell lymphomas (PTCL-NOS = 133 patients) who underwent allo-HCT, with 69% receiving transplant in the R/R setting. The 5-year PFS and OS were 40% and 51%, respectively, with improved PFS for patients who achieved CR2 prior to allo-HCT. An international collaboration between the Center for International Blood and Marrow Transplant Research and European Bone Marrow Transplantation Group (EBMT) registries reported outcomes from 1942 patients with ALCL, AITL, or PTCL-NOS (N = 963) treated with allo-HCT consolidation using various donor sources. The 3-year PFS and OS were 48%-52% and 60%-64%, respectively, with no differences in outcomes based on graft types.[47] Shumilov et al[48] presented another EBMT registry report showing a 2-year PFS and OS of 55.7% and 66.1% in patients in CR2, with similar survival after allo-HCT whether patients received two lines or ≥3 lines of prior therapy (2-year OS, 59.3%-68.6%, $P = .22$).

The choice of second-line therapy should depend on whether the goal is curative with allo-HCT or palliative with disease control and improved quality of life (QoL). For fit patients without chemo-refractory disease who may undergo allo-HCT, combination chemotherapy could increase the odds of achieving CR, which correlates with better post-transplant outcomes. For patients receiving palliative treatment, single-agent therapies are preferred to maximize QoL and minimize toxicities, especially in those achieving clinically meaningful and durable responses who can potentially receive maintenance therapy depending on the ongoing effectives and side effects.

Several combination chemotherapy regimens have been evaluated in phase II trials and retrospective studies. A small retrospective study (N = 31) showed that Dexa-BEAM had better outcomes than ifosfamide, carboplatin, etoposide in R/R T-cell lymphomas, with ORRs of 69% versus 64% and CRs of 38% versus 7%, respectively. PFS was also superior with Dexa-BEAM (6.4 *v* 2 months, $P = .01$).[49] The GDP regimen (Gemcitabine, Dexamethasone, and Cisplatin) showed ORRs between 64% and 72% and median PFS between 5 and 9 months.[50,51] Other combinations, including ESHAP, DHAP (dexamethasone, cisplatin, cytarabine), GEMOX, and GVP, have been assessed in small retrospective studies, showing ORRs of 32%-68% and CRs of 9%-29%, with the longest PFS observed in patients proceeding to HCT.[52-56] Bendamustine as a single agent was evaluated in a phase II trial of 60 patients with R/R T-cell lymphomas, showing an ORR and CR of 50% and 28%, respectively, with median PFS and OS of 3.6 and 6.2 months.[57] In non-ALCL R/R PTCL with CD30 expression, BV activity is modest (ORR, 21%-33%).[58,59,64]

Several novel agents show promising single-agent activity in R/R T-cell lymphomas. Histone deacetylase inhibitors (HDACis) are particularly effective in lymphomas driven by epigenetic mutations (eg, IDH2-DNMT3A-TET2). Currently, belinostat (Food and Drug Administration [FDA]–approved) and chidamide (approved in China) are the only approved HDACis, although romidepsin remains in the National Comprehensive Cancer Network guidelines and is a viable option. Belinostat, a pan-HDACi, was FDA-approved in R/R PTCL based on the BELIEF phase II trial (N = 120) that included patients with several T cell lymphomas (64.2% PTCL-NOS) and showed ORR and CR of 25.8% and 10.8%. Median PFS and OS were 1.6 and 7.9 months, with a DoR of 13.6 months in responders.[60] A smaller prospective phase II trial of 24 R/R PTCL patients showed similar ORR/CR (25%/8.3%).[61] A phase III confirmatory trial of belinostat (SPI-BEL-301; ClinicalTrials.gov identifier: NCT0607213) is ongoing. Romidepsin received accelerated FDA approval in 2011 based on a phase II trial of 130 patients (53% PTCL-NOS). The ORR and CR were 25% and 15%. The phase III LUMIERE study with ORR and CR of 61% and 33%.[62] Phase III study of CHOP+/Romidepsin for treatment-naïve PTCL failed to meet its primary end point of PFS,[63] neither after median follow-up of 6 years.[64] Based on these results romidepsin was voluntarily removed from the market in 2021, but recent empirical evidence shows that it continues to be used in the United States.[65] Other agents targeting similar post-translational mechanisms such as hypomethylating agents (eg, 5-azacitidine) have demonstrated single-agent activity

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TABLE 1. Drugs Under Study for the Treatment of R/R PTCL-NOS

Molecule	Phase	Results	Common Adverse Events	Reference
Darinaparsin	II	ORR: 9.3%, tumor reduction: 62.3%, OS: 17.4 months, PFS: 3.3 months in the overall population, and 7.5 months in patients who responded	Anemia, thrombocytopenia, hypertension	[76]
Duvelisib (oral dual inhibitor of δ/γ isoforms of phosphatidylinositol 3-kinase)	I	ORR: 50%, CR: 18.8%, PFS: 8.3 months	Neutropenia, transaminase elevation, diarrhea	[77]
Panobinostat (HDAC inhibitor)	II	ORR: 17%, DoR: 3.7 months	Cytopenias, diarrhea, fatigue (>20%)	[78]
Alisertib (aurora kinase A inhibitor)	II	ORR: 30%, CR: 3%, PFS: 3.7 months	Neutropenia, mucositis, fatigue	[79]
HH2853 (EZH1/2 inhibitor)	Ib	ORR: 60.7%, CR: 21.4%	Thrombocytopenia (48.6%), anemia (51.4%), diarrhea (40.5%), rash, asthenia	[80]
Mogamulizumab (humanized monoclonal anti-CCR4 antibody)	I/II	ORR: 11%, DoR: 8.4 months, PFS: 2.1 months	Cytopenias, fever, rash, infusion reaction	[81]
Golidocitinib (selective oral JAK1 inhibitor)	II	ORR: 44.3%, CR: 24%, PR: 20%, DoR: 20.7 months, PFS: 5.6 months	Grade 3-4 Neutropenia (29%), leukopenia (26%), lymphopenia (21%), thrombocytopenia (20%)	[82]

Abbreviations: CR, complete response; DoR, duration of response; HDAC, histone deacetylase; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; R/R, relapsed/refractory.

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in these lymphomas.[66] The combination of romidepsin and oral 5-azacitidine showed remarkable high activity in a small phase II trial where 23 patients with PTCL-NOS were treated with this approach (10 treatment-naïve and 13 R/R disease).[67] The ORR and CR were 61% and 48%, median PFS and OS in the R/R patients was 8 and 20.6 months. Pralatrexate, an antifolate chemotherapeutic agent with high affinity for the reduced folate carried,[68] received FDA accelerated approval for R/R PTCL based on the PROPEL phase II trial which enrolled 111 R/R PTCL patients (53% PTCL-NOS), showing ORR and CR of 29% and 10%, in the treated patients (N = 109). The median progression free survival, DoR, and OS were 3.5, 10.1, and 14.5 months, respectively.[69] Pralatrexate was one of the agents on the control arms of the phase III LUMIERE study and again demonstrated clinical activity with ORR and CR or 43% and 27%.[69] Other options described in patients with R/R PTCL are summarized in Table 1.

Recommendations:

- Early referral for allo-HCT is recommended for patients with primary refractory disease, early relapse (within 6 months of CR1), or relapse following ASCT, to enable timely human leukocyte antigen typing and donor identification in eligible transplant candidates.
- Use a non–cross-resistant multiagent chemotherapy regimen for patients with chemo-sensitive disease to achieve CR followed by allo-HCT.
- Allo-HCT is recommended for those with either a primary refractory or relapsed disease after autologous SCT.
- Promote the inclusion of patients in clinical trials evaluating novel therapies.

TABLE 2. Summary of Radiotherapy Indications, Doses, and Fractionation in PTCL-NOS

Clinical Scenario	Recommended Dose/Fractionation	Notes
Stage I (favorable prognostic score) consolidation after CR or PR[83]	30 Gy in 15-17 fractions (1.8-2.0 Gy per fraction)	ISRT to the involved site; consider after abbreviated chemotherapy (3-4 cycles) in selected early-stage cases
Residual macroscopic disease (pre-ASCT consolidation or in advanced disease)[83]	36-40 Gy in 1.8-2.0 Gy fractions	Higher dose recommended for gross residual disease after induction chemotherapy
Symptom palliation or refractory/relapsed disease[83]	20-30 Gy in 5-10 fractions (hypofractionated schedules acceptable)	Focus on quality of life and rapid symptom relief; shorter courses preferred in the palliative setting
Early-stage disease (selected favorable cases)[83]	30-36 Gy (consolidative after chemotherapy)	Can be considered in combination with abbreviated systemic therapy in limited-stage patients with favorable features

NOTE. (1) Doses and fractionation are adapted from current evidence and international guidelines, including recommendations from the ILROG. (2) IMRT or other advanced techniques should be used whenever possible to minimize toxicity to surrounding organs at risk. (3) In resource-limited settings, 3D conformal radiotherapy remains acceptable when IMRT is not available. (4) For palliative intent, hypofractionated schedules (eg, 20 Gy in five fractions or 30 Gy in 10 fractions) are appropriate to improve patient convenience and quality of life.
Abbreviations: ASCT, autologous stem-cell transplantation; CR, complete response; Gy, Gray; ILROG, International Lymphoma Radiation Oncology Group; IMRT, intensity-modulated radiotherapy; ISRT, involved-site radiotherapy; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

TABLE 3. Markers for IHC and Their Purpose in PTCL-NOS Diagnosis

Marker/Panel	Purpose	Specific Details	References
Pan-T-cell panel (CD2, CD3, CD5, CD7)	Confirm T-cell lineage and detect aberrant antigen loss to support clonality	Essential for accurate classification; routine inclusion in diagnostic workup	3,84
T-cell subtype markers (CD4, CD8)	Identify clonal populations and guide subsequent diagnostic studies	Detects aberrant phenotypes (eg, double-positive or double-negative profiles)	3,84
CD30 and ALK	Identify candidates for targeted therapies (eg, brentuximab vedotin)	Systematic evaluation in all cases, particularly for CD30-positive subtypes	3,84
Cytotoxicity markers (TIA-1, granzyme B, perforin)	Support diagnosis of cytotoxic phenotypes	Essential for MEITL or EATL; TIA-1 is most sensitive, granzyme B and perforin enhance specificity	3,84
TFH markers (PD-1, ICOS, CXCL13, CD10, BCL6)	Identify PTCL with the TFH phenotype	Requires expression of at least two TFH markers to distinguish from B-cell lymphomas or reactive infiltrates	3,84
Ki-67 proliferation index	Estimate tumor proliferation and guide therapeutic decisions	High expression (>30%) associated with worse prognosis; assess semiquantitatively	3,84
Bone marrow IHC (CD3, CD4, CD8, Ki-67)	Detect marrow infiltration	Recommended in all confirmed PTCL cases; not always evident with H&E staining	3,84
Skin IHC panel (CD3, CD4, CD8, CD30, CXCL13, BCL6, ICOS)	Differentiate primary *v* secondary skin involvement	Distinguishes primary cutaneous T-cell lymphomas (eg, mycosis fungoides) from secondary TFH phenotype involvement	3,84
Differential markers (CD20, PAX5, CD68)	Rule out B-cell lymphomas or inflammatory conditions	Recommended for atypical morphology or mixed infiltrates to prevent diagnostic errors	3,84
CD56	Refine classification in extranodal or NK/T-cell lymphoma patterns	Evaluate in cases with extranodal involvement or suggestive morphology	3,84

Abbreviations: ALK, anaplastic lymphoma kinase; EATL, enteropathy-associated T-cell lymphoma; IHC, immunohistochemistry; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; TFH, T follicular helper.

- Use of HDACi and pralatrexate monotherapy can be considered and are preferred agents for unfit or chemotherapy-refractory patients.

Question 10: What Is the Role of RT in the Treatment of PTCL-NOS?

Outcomes with radiation therapy (RT) in the setting of stable or progressive disease after systemic therapies for induction are generally favorable, but data from literature about it is scarce. Small retrospective studies of adjuvant RT for early-stage disease have shown mixed results. A single-institutional retrospective analysis reported superior 3-year OS and PFS when RT was added to chemotherapy in patients with stages I and II (50% *v* 23% for OS and 33% *v* 15% for PFS).[70] A retrospective study from the International Peripheral T-cell Lymphoma Project[4] showed higher OS and failure-free survival in patients with stage I who received

TABLE 4. Markers for Flow Cytometry and Their Purpose in PTCL-NOS Diagnosis

Marker/Panel	Purpose	Specific Details	References
Pan-T-cell markers (CD2, CD3, CD5, CD7)	Confirm T-cell lineage and detect aberrant antigen loss	Essential for identifying T-cell neoplasms and supporting clonality; used in initial multiparametric screening	3,7,84
T-cell subtype markers (CD4, CD8)	Identify clonal populations and guide subtype classification	Detects aberrant phenotypes (eg, double-positive or double-negative profiles) to refine diagnosis	3,7,84
Activation markers (CD25, HLA-DR, CD38)	Assess tumor cell activation status	Supports characterization of PTCL immunophenotype and risk stratification	3,7,84
Cytotoxicity markers (TIA-1, granzyme B, perforin)	Identify cytotoxic phenotypes	Critical for subtypes like MEITL or EATL	3,7,84
Memory markers (CD27, CD28)	Evaluate T-cell memory status	Contributes to immunophenotypic profiling and understanding tumor biology	3,7,84
Maturation markers (CD45RO, CD45RA, CCR7)	Assess T-cell maturation stage	Aids in distinguishing neoplastic from reactive T-cell populations	3,7,84
Clonality markers (TCR-γδ, TRBC1)	Confirm T-cell clonality	Could enhance diagnostic precision by identifying clonal T-cell receptor expression	3,7,84
Disease-specific markers (CD26, CD30, CD279/PD-1, CD10, TCL1)	Refine subtype classification	CD26 (mycosis fungoides), CD30 (anaplastic large cell lymphoma), CD279/PD-1 and CD10 (angioimmunoblastic T-cell lymphoma), TCL1 (T-prolymphocytic leukemia)	3,7,84

Abbreviations: EATL, enteropathy-associated T-cell lymphoma; HLA, human leukocyte antigen; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

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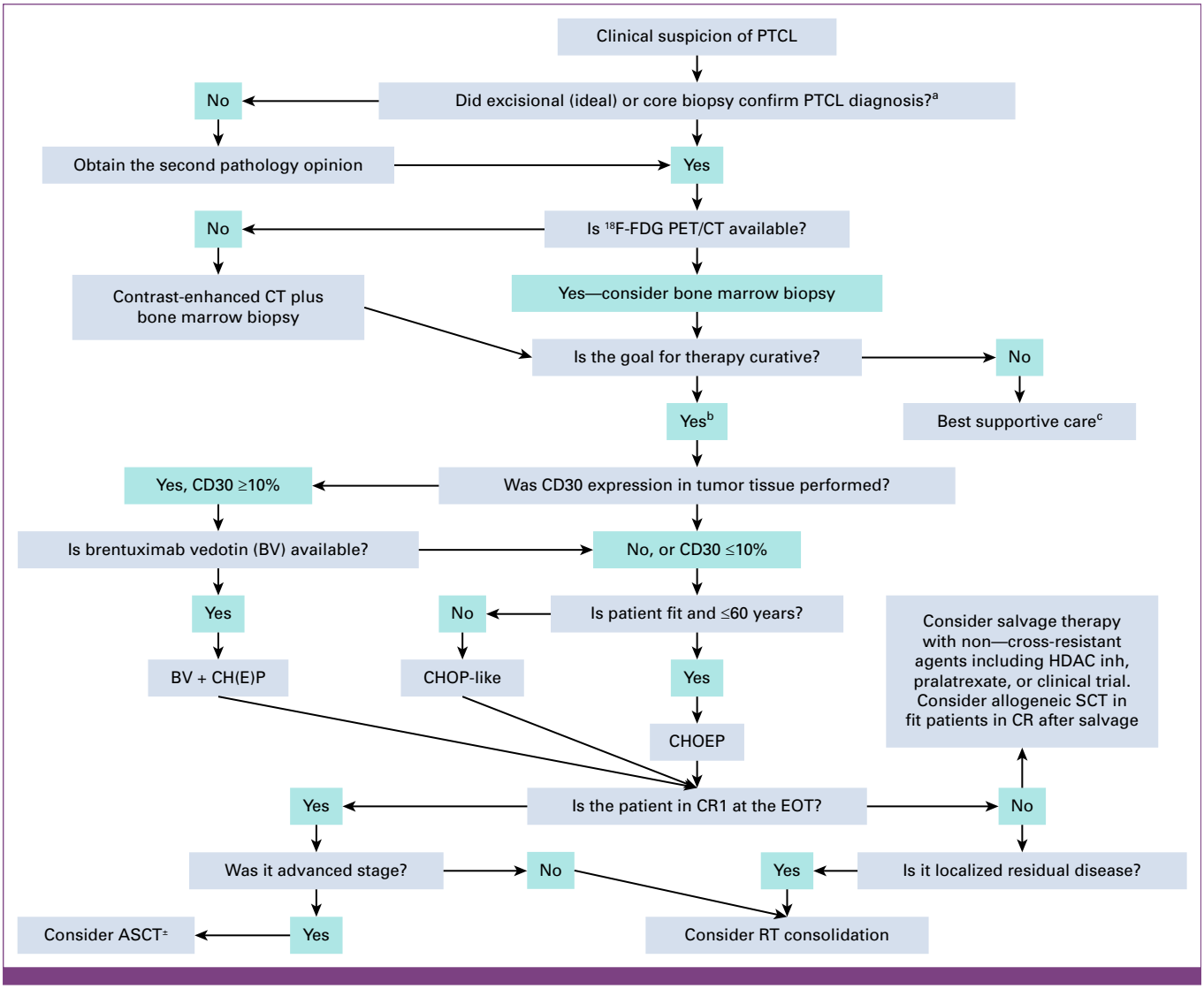


FIG 2. Proposed approach for PTCL-NOS in Latin America. The algorithm summarizes the consensus recommendations for diagnosis, staging, risk stratification, first-line treatment selection (including resource-adapted options), response assessment, consolidation with autologous or allogeneic stem-cell transplantation, radiotherapy indications, follow-up, and management of relapsed/refractory PTCL-NOS. Preferred approaches are shown in solid boxes; resource-limited alternatives are indicated where applicable. [a]A limited IHC and/or flow cytometry capabilities should include markers to confirm mature T-cell lineage while excluding major mimics (eg, IHC panel = CD3, CD20 or PAX5, CD4, CD8, CD5 and/or CD7, Ki-67, and, if available, CD30 and ALK; flow panel = CD45, CD3, CD2, CD5, CD7, CD4, CD8, and CD19/CD20, with CD56 if available for NK/T-cell lymphoma detection). [b]Participation in clinical trials or expanded-access programs is recommended whenever possible. [c]Consider dose-attenuated approaches (eg, mini-CHOP-like therapy) if feasible. If cancer-related pain, consider palliative radiation. Early referral to palliative care is highly recommended. With or without ASCT in CR1 for eligible patients with early referral for ASCT in primary refractory or post-ASCT relapses. ALK, anaplastic lymphoma kinase; ASCT, autologous stem-cell transplant; CR, complete response; CR1, CR after first-line therapy; EOT, end of therapy; HDAC, histone deacetylase; IHC, immunohistochemistry; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; RT, radiation therapy.

chemotherapy followed by RT compared with those receiving chemotherapy alone. A report from the Swedish Lymphoma registry[8] showed a trend toward better 5-year OS in 32 patients who received RT after chemotherapy compared with 118 patients treated with chemotherapy only (73% *v* 53%; HR, 0.58 [95% CI, 0.32 to 1.05]) and improved 5-year PFS (60% *v* 45%; HR, 0.57 [95% CI, 0.32 to 1.03]). Otherwise, two small retrospective series showed no benefit in addition of RT in the management of early stages.[71,72] Database from the SEER and from two high-capacity cancer centers in China identified between 2000 and 2016, among 844 patients with early-stage disease, 27.6% received RT and 6.8% of the 1,924 patients with advanced-stage. In the early-stage subgroup, the use of RT was significantly associated with an improvement in OS (58.5% *v* 35.1%, $P < .001$) and disease-specific survival (DSS) (66.3% *v*

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44.0%, $P < .001$). No survival benefit of RT was observed in patients with advanced-stage disease (5-year OS rate of 28.7% *v* 24.4%, $P = .089$ and 5-year DSS rate of 32.9% *v* 31.3%, $P = .223$).[73]

In the setting of partial response or progressive disease after systemic therapy in advanced disease, RT has been recommended as consolidation therapy by international guidelines despite the absence of prospective and randomized trials.[74] Further prospective studies with more comprehensive data are needed to evaluate the effectiveness and toxicity of RT. The dose of RT to consolidate a CR should be 30 Gy in 15-17 daily fractions, in the region of pre-CT tumor volume. For macroscopic residual disease after induction chemotherapy, doses in the range of 36-40 Gy should be used from 1.8 to 2.0 Gy daily fractions. For symptoms relief hypofractionation schedule can be used, as 20 Gy in five daily fractions or 30 Gy in 10 daily fractions.[75] Intensity-modulated delivered dose technique should be always tried to be employed due to its more dose concentration capacity than 3-D conformal technique. A summary of recommendations regarding RT is shown in Table 2.

Recommendations

- *Stage I with favorable prognostic score:* RT to consolidate complete or partial responses.
- *Advanced-stage or adverse prognostic score*: RT before ASCT in patients with partial response after induction therapy.
- *Symptom relief*: RT can be used for symptom relief as a component of management for R/R PTCL or for palliation.

Question 11: What Is the Role of IHC and FC in the Diagnosis and Follow-Up?

The diagnostic approach to PTCL in adults requires the systematic and evidence-based use of IHC due to the morphological and phenotypic complexity of these neoplasms. Table 3 summarizes the recommendations based on current evidence. Flow cytometry (FC) is an essential and complementary tool for diagnosis and monitoring, offering the ability to simultaneously analyze multiple markers for detailed immunophenotypic characterization of tumor cells, distinguishing T-cell from B-cell lymphomas and reactive processes with high sensitivity, as well as identifying immunophenotypic profiles associated with aggressive disease behavior.[3] A multiparametric screening panel should be employed, as shown in Table 4.[2] During follow-up, FC demonstrates superior sensitivity (>95%) compared to IHC for detecting minimal residual disease in bone marrow, peripheral blood, or body fluids, enabling early relapse detection and dynamic treatment monitoring.

SUMMARY OF RESOURCE-ADAPTED RECOMMENDATIONS FOR LATIN AMERICA

Figure 2 summarizes our proposed approach for PTCL-NOS in LATAM. Recognizing the heterogeneous availability of health care resources across LATAM, the panel provides a summary of the preferred approaches versus feasible alternatives in resource-limited settings:

Preferred and ideal approach:

- PET/CT for staging and response assessment (with TMTV evaluation). BMB should be considered.
- Full IHC + FC panels are outlined in Tables 2 and 3.
- BV-based therapy for CD30$^+$ (≥10%) PTCL-NOS.
- CHOEP for fit patients 60 years and younger.
- Interim and EOT PET/CT.
- ASCT in CR1 for eligible patients with early referral for ASCT.
- Participation in clinical trials or expanded-access programs whenever possible.

Resource-limited alternatives:

- Contrast-enhanced CT for staging and response assessment. BMB is highly recommended.
- IHC and/or FC capabilities to confirm mature T-cell lineage and excluding major mimics (eg, IHC panel = CD3, CD20 or PAX5, CD4, CD8, CD5 and/or CD7, Ki-67, and if available CD30 and ALK; flow panel = CD45, CD3, CD2, CD5, CD7, CD4, CD8, and CD19/CD20, with CD56 if available for NK/T-cell lymphoma detection).
- CHOP-21 when etoposide or BV are not readily available (treatment should not be delayed in symptomatic/high tumor burden patients).
- Clinical and laboratory monitoring with CT at 6-12-24 months when serial PET/CT is not feasible.
- Early referral to regional centers with transplant capability is recommended.
- Participation in clinical trials or expanded-access programs whenever possible.

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AFFILIATIONS

[1]Department of Hematology/Oncology, Clínica Central del Eje, Pereira, Colombia
[2]Centro de Investigación Hemato Oncológico (CIHO), IDC Instituto de Cáncer Hemato Oncólogos, Cali, Colombia
[3]Instituto Nacional de Cancerología de Colombia (INC), Bogotá, Colombia
[4]Hospital Militar Central, Bogotá, Colombia
[5]Universidad Pontificia Bolivariana (UPB), Medellín, Colombia
[6]Unidad de Hemato-Oncología 360, Clínica Santa Sofía, IOH-Universidad Central de Venezuela, Caracas, Venezuela
[7]Servicio de Oncología Médica, Hospital Edgardo Rebagliati Martins, Instituto de Ciencias Biomédicas, Universidad Ricardo Palma, Lima, Perú
[8]Hospital Dr Fernando Ocaranza, ISSSTE, Hermosillo, Mexico
[9]Hospital Británico, CASMU, Montevideo, Uruguay
[10]Departamento de Hematología, Hospital Central del Instituto de Previsión Social (IPS), Asunción, Paraguay

[11]Hospital del Salvador, Santiago, Chile
[12]Hospital Británico de Buenos Aires, Buenos Aires, Argentina
[13]Hospital Seton de la Caja Petrolera de Salud, Clínica Los Olivos, Cochabamba, Bolivia
[14]Hospital Universitario Dr José Eleuterio González de la Universidad Autónoma de Nuevo León (UANL), Monterrey, Mexico
[15]Hospital Ángeles del Pedregal, México City, Mexico
[16]Hospital Metropolitano, Quito, Ecuador
[17]Hospital Dr Luis Díaz Soto, La Habana, Cuba
[18]Hospital de Apoyo II-2 de Sullana, Piura, Peru
[19]Hospital Israelita Albert Einstein, Sao Paulo, Brasil
[20]Hospital Alemão Oswaldo Cruz, Hospital das Clínicas, Instituto do Câncer do Estado de São Paulo (ICESP), Sao Paulo, Brasil
[21]BP—A Beneficência Portuguesa de São Paulo, Sao Paulo, Brasil
[22]Hospital Nacional Edgardo Rebagliati Martins & Centro de Investigación de Medicina de Precision, Universidad San Martin de Porres, Lima, Peru
[23]Instituto de Previsión Social, Asunción, Paraguay
[24]Fundación Cardiovascular de Colombia (FCV), Hospital Internacional de Colombia (HIC), Piedecuesta, Colombia
[25]Hematooncologos Isabel Matilde Chinchia Arias SAS, Cali, Colombia
[26]Hospital Internacional de Colombia (HIC), Bogota, Colombia
[27]Hospital de San Jose, Bogotá, Colombia
[28]Hospital Sagrado Corazón, Instituto de Trasplante de Alta Complejidad, Buenos Aires, Argentina
[29]Centro Medico Nacional "20 de Noviembre"—ISSSTE, México City, Mexico
[30]Hospital Alcívar y Hospital Clínica Kennedy—Samborondón, Guayaquil, Ecuador
[31]Hospital Clinico Quirurgico Hermanos Ameijeiras, La Habana, Cuba
[32]Instituto de Hematologia e Inmunologia (IHI), La Habana, Cuba
[33]Hospital de Emergencias Villa El Salvador (HEVES), Instituto de Ciencias Biomédicas, Universidad Ricardo Palma, Lima, Peru
[34]San Juan del Cesar, La Guajira, Colombia
[35]BP—Hospital BP Paulista, Sao Paulo, Brasil
[36]Hospital Federico Lleras Acosta, Ibagué, Colombia
[37]Moffitt Cancer Center, Pembroke Pines, FL
[38]Santa Casa Medical School, Sao Paulo, Brazil
[39]Bing Center for Waldenstrom Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA
[40]MD Anderson Cancer Center, Houston, TX

CORRESPONDING AUTHOR

Luis Malpica, MD; e-mail: lemalpica@mdanderson.org.

EQUAL CONTRIBUTION

H.I.Q. and J.E.G.-R. contributed equally to this work.

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AUTHOR CONTRIBUTIONS

Conception and design: Henry Idrobo Quintero, Juan Esteban Garcia-Robledo, Juan Alejandro Ospina, Humberto Martínez-Cordero, Maria Alejandra Torres Viera, Brady Ernesto Beltran, Ana Carolina Oliver, Rosa Oliday Ríos-Jiménez, Rafael Pichardo-Rodriguez, Guilherme Fleury Perini, André Abdo, Cristobal Augusto Frutos, Jhon Alexander Avila-Rueda, Ana Milena Cantillo Garcia, Jenny Niño-Galvis, Carlos Fernando Gómez-Calcetero, César Abad De la Hoz, Eleazar Hernández-Ruiz, Jose Manuel Vela-Ruiz, Edgar Fabián Manrique-Hernández, Robson Ferrigno, Silvana Orozco, Carlos Chiattone
Administrative support: Henry Idrobo Quintero, Juan Esteban Garcia-Robledo, Lina María Martinez-Correa, Sally Paredes-Noguni, Jose Manuel Vela-Ruiz, Silvana Orozco, Luis Malpica
Provision of study materials or patients: Henry Idrobo Quintero, Luis Villela, Ana Carolina Oliver, German Stemmelin, Jose Macias, Rosa Oliday Ríos-Jiménez, Danielle Leão Cordeiro de Farias, Sally Paredes-Noguni, César Abad De la Hoz, Eleazar Hernández-Ruiz, Francisca Ramírez, Jorge Ernesto Muñio-Perurena, Yamile Quintero-Sierra, Leandro Francisco Barrios, Carlos Chiattone
Collection and assembly of data: Henry Idrobo Quintero, Juan Esteban Garcia-Robledo, Juan Alejandro Ospina, Lina María Martinez-Correa, Maria Alejandra Torres Viera, Brady Ernesto Beltran, Luis Villela, Ana Carolina Oliver, Alana von Glasenap, German Stemmelin, Jose Macias, Perla R. Colunga-Pedraza, Myrna Candelaria, Marcela Zamora, Rosa Oliday Ríos-Jiménez, Rafael Pichardo-Rodriguez, Guilherme Fleury Perini, André Abdo, Danielle Leão Cordeiro de Farias, Denisse Castro Uriol, Sally Paredes-Noguni, Cristobal Augusto Frutos, Jhon Alexander Avila-Rueda, Ana Milena Cantillo Garcia, Isabel Matilde Chinchia, Jenny Niño-Galvis, Carlos Fernando Gómez-Calcetero, Eleazar Hernández-Ruiz, Jaiver Alexander Fonseca, Jorge Ernesto Muñio-Perurena, Yamile Quintero-Sierra, Jose Manuel Vela-Ruiz, Leandro Francisco Barrios, Edgar Fabián Manrique-Hernández, Silvana Orozco, Jose Sandoval-Sus, Carlos Chiattone, Bryan Valcarcel
Data analysis and interpretation: Henry Idrobo Quintero, Juan Alejandro Ospina, Brady Ernesto Beltran, Luis Villela, Ana Carolina Oliver, Macarena Roa, Guilherme Fleury Perini, André Abdo, Denisse Castro Uriol, Sally Paredes-Noguni, Cristobal Augusto Frutos, Jhon Alexander Avila-Rueda, Ana Milena Cantillo Garcia, Isabel Matilde Chinchia, Eleazar Hernández-Ruiz, Francisca Ramírez, Jose Manuel Vela-Ruiz, Edgar Fabián Manrique-Hernández, Silvana Orozco, Jose Sandoval-Sus, Carlos Chiattone, Jorge Castillo, Luis Malpica
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Humberto Martínez-Cordero
Honoraria: Janssen, Sanofi, Bristol Myers Squibb/Celgene, Takeda
Consulting or Advisory Role: Janssen, Sanofi, Bristol Myers Squibb/Celgene, Takeda
Travel, Accommodations, Expenses: Sanofi

Lina María Martinez-Correa
Employment: Riesgo de Fractura S.A.

Alejandra Torres Viera
Speakers' Bureau: Takeda
Travel, Accommodations, Expenses: Roche/Genentech, Tutteur

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Luis Villela
Honoraria: Roche, BeOne, AstraZeneca Mexico, J&J Mexico
Speakers' Bureau: Roche, AbbVie Mexico, Merck Sharp & Dome Mexico, J&J, BeOne

Ana Carolina Oliver
Consulting or Advisory Role: Janssen, Roche, AbbVie
Speakers' Bureau: AbbVie
Travel, Accommodations, Expenses: Adium Pharma

Macarena Roa
Honoraria: AbbVie, AstraZeneca
Travel, Accommodations, Expenses: Roche

Perla R. Colunga-Pedraza
Consulting or Advisory Role: Knight Therapeutics/Biotoscana, Takeda
Speakers' Bureau: Knight Therapeutics/Biotoscana, Takeda
Travel, Accommodations, Expenses: Janssen

Marcela Zamora
Travel, Accommodations, Expenses: Roche

Guilherme Fleury Perini
Honoraria: Janssen, Takeda, AstraZeneca, BeiGene
Consulting or Advisory Role: Janssen, AstraZeneca
Speakers' Bureau: AbbVie, Janssen
Travel, Accommodations, Expenses: Janssen

Danielle Leão Cordeiro de Farias
Consulting or Advisory Role: Janssen, Novartis, Amgen, Bristol Myers Squibb, Roche, AbbVie, Libbs, Celgene, Eurofarma, Knight Therapeutics
Speakers' Bureau: Janssen, Roche, AbbVie, AstraZeneca, Lilly, Pfizer, Takeda, Sanofi, Knight Therapeutics
Research Funding: Pfizer (Inst), Janssen (Inst), Libbs (Inst), AbbVie (Inst), Sanofi (Inst), AstraZeneca (Inst), Lilly (Inst), Regeneron (Inst), IPSEN (Inst), ADC Therapeutics (Inst)
Travel, Accommodations, Expenses: Libbs, AbbVie, Takeda, Roche, Janssen, Knight Therapeutics, Janssen Oncology

Sally Paredes-Noguni
Honoraria: Johnson & Johnson/Janssen
Speakers' Bureau: Johnson & Johnson/Janssen
Research Funding: MSD

Cristobal Augusto Frutos
Employment: Medac
Consulting or Advisory Role: Boller S.A.

Isabel Matilde Chinchia
Consulting or Advisory Role: Janssen Oncology, Roche, AbbVie
Speakers' Bureau: Janssen Oncology, Roche, Bristol Myers Squibb/Celgene, AstraZeneca

Eleazar Hernández-Ruiz
Speakers' Bureau: Roche
Research Funding: Bristol Myers Squibb, Amgen, Roche

Jaiver Alexander Fonseca
Stock and Other Ownership Interests: AstraZeneca
Consulting or Advisory Role: Roche, Novartis
Speakers' Bureau: Johnson & Johnson/Janssen, AstraZeneca, Amgen, Sanofi
Travel, Accommodations, Expenses: Johnson & Johnson/Janssen, Amgen

Leandro Francisco Barrios
Honoraria: AstraZeneca
Travel, Accommodations, Expenses: Jonson

Jose Sandoval-Sus
Consulting or Advisory Role: Pfizer, ADC Therapeutics, Acrotech Biopharma, Kite, a Gilead company, Genentech, Roche
Speakers' Bureau: Pfizer
Travel, Accommodations, Expenses: Kite/Gilead, Genentech, Roche

Carlos Chiattone
Consulting or Advisory Role: Roche, Takeda, Janssen, Pint Pharma

Jorge Castillo
Consulting or Advisory Role: Janssen, Beigene, AbbVie/Pharmacyclics, Cellectar, Loxo/Lilly, MustangBio, Nurix
Research Funding: Pharmacyclics (Inst), Abbvie (Inst), BeiGene (Inst), Loxo/Lilly (Inst)

Luis Malpica
Research Funding: Dizal Pharma (Inst)

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